Review

Batzella, Crambe and Monanchora: Highly Prolific Marine Sponge Genera Yielding Compounds with Potential Applications for Cancer and Other Therapeutic Areas

Amr El-Demerdash 1,2,*; Atanas G. Atanasov 3,4,*; Anupam Bishayee 5,*; Mamdouh Abdel-Mogib 2; John N. A. Hooper 6 and Ali Al-Mourabit 1

1 Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Univ. Paris-Sud, University of Paris-Saclay, 1, Avenue de la Terrasse, 91198 Gif-Sur-Yvette, France; Ali.ALMOURABIT@cnrs.fr
2 Organic Chemistry Division, Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt; mmdhbdlimgb@gmail.com
3 Institute of Genetics and Animal Breeding of the Polish Academy of Sciences, 05-552 Jastrzebiec, Poland
4 Department of Pharmacognosy, University of Vienna, 1090 Vienna, Austria
5 Department of Pharmaceutical Sciences, College of Pharmacy, Larkin University, 18301 N. Miami Avenue, Miami, FL 33169, USA
6 Queensland Museum, P.O. Box 3300, South Brisbane, QLD BC 4101, Australia; john.hooper@qm.qld.gov.au
* Correspondence: eldemerdash555@gmail.com (A.E.-D.); atanas.atanason@univie.ac.at (A.G.A.); abishayee@ularkin.org or abishayee@gmail.com (A.B.); Tel.: +0033-758-490-229 (A.E.-D.); Tel.: +0048-227-367-022 (A.G.A.); Tel.:+1-305-760-7511 (A.B.)

Received: 1 November 2017; Accepted: 22 December 2017; Published: 2 January 2018

Abstract: Pyrroloquinoline and guanidine-derived alkaloids present distinct groups of marine secondary metabolites with structural diversity that displayed potentialities in biological research. A considerable number of these molecular architectures had been recorded from marine sponges belonging to different marine genera, including Batzella, Crambe, Monanchora, Clathria, Ptilocaulis and New Caledonian starfishes Fromia monilis and Celerina heffernani. In this review, we aim to comprehensively cover the chemodiversity and the bioactivities landmarks centered around the chemical constituents exclusively isolated from these three marine genera including Batzella, Crambe and Monanchora over the period 1981–2017, paying a special attention to the polycyclic guanidinic compounds and their proposed biomimetic landmarks. It is concluded that these marine sponge genera represent a rich source of novel compounds with potential applications for cancer and other therapeutic areas.

Keywords: marine sponges; Poecilosclerida; Batzella; Crambe; Monanchora; guanidine alkaloids; pyrroloquinoline alkaloids; bioactivities; biomimetic synthesis

1. Introduction

As a result of the rise of many current medical challenges, including hepatitis, parasitic infection, lifestyle-induced diseases, such as diabetes, hypertension, many forms of cancer, multi-drug resistance pathogens and other diseases, searching for new bioactive compounds with novel modes of action is necessary. Marine natural products represent potent, promising and sustainable sources for biomedications [1]. Up to present time, eight marine-derived drugs were approved for market pipelines for the treatment of some of these current medical challenges [2,3]. Marine sponges (phylum Porifera), even though they are the most primitive class within the animal kingdom, are considered renewable powerful suppliers for bioactives. The marine genera belonging to the
order Poecilosclerida, Batzella (family Chondropsidae), Crambe and Monanchora (family Crambeidae), are rich in the production of highly physiologically active pyrroloquinoline and guanidine-derived alkaloids [4–6], with a vast scope of biological potentialities including cytotoxic and antiviral [7–12], HIV-1 inhibitors [13,14], enzyme inhibitors [15], receptor antagonist [16], Ca2+ channel blocker [17], antifungal [18] and antimicrobial [19–21]. These interesting compounds are considered taxonomic markers in particular for some Poecilosclerida and Axinellida marine sponge genera [5]. Their complex molecular architectures and potent biological activities have made them for years ideal target molecules for synthetic applications [22–28]. Beside the production of guanidine-derived architectures, some deep-water species of Batzella produced pyrroloquinoline-derived alkaloids, which raises a chemotaxonomic question about the systematic relatedness of this genus (family Chondropsidae) to other genera like Crambe and Monanchora (family Crambeidae). A chemosystematic exploration has revealed that Batzella sponges containing cyclic guanidine alkaloids are chemically and taxonomically similar, and perhaps synonymous with, Monanchora and Crambe. However, the deep-water Batzella sponges produced pyrroloquinoline alkaloids is taxonomically unrelated to the Batzella previously mentioned. Chemically, it is almost similar to the Zyzzya and Latrunculia marine sponges but their phylogenetic relationship is still undetermined [29]. Systematically, the World Porifera Database accepts nine valid species of Batzella [30], nine valid species in the genus Crambe [31] and fourteen valid species currently in the genus Monanchora [32]. To the best of our knowledge, previous chemical investigations of Batzella was centered on only a single unidentified species from Madagascar [33], for the genus Crambe only one identified species, the type species Crambe crambe from the Mediterranean [34] and finally five identified Monanchora species including Monanchora unguiculata [35], Monanchora dianchora [36], Monanchora pulchra [37], Monanchora arbuscula [38] and Monanchora unguifera [35] in addition to one unidentified species of Monanchora n. sp. [39].

2. Chemistry and Biology of Natural Products Isolated from Batzella, Crambe and Monanchora

In this review, we provide comprehensive insights on the previous chemical and biological reports for the metabolites of the three marine genera. To facilitate the handling of this survey, the isolated natural compounds are classified by their polycyclic skeleton coupled with their recorded biological potentialities whenever applicable.

2.1. Piperidine Iminosugars Alkaloids

(++)-Batzellasides A–C (1–3), three alkylated piperidine iminosugars were isolated from a Madagascar sponge, Batzella sp. and represented the first naturally occurring marine iminosugars. These compounds demonstrated inhibition of the growth of Staphylococcus epidermidis with MICs (Minimum Inhibitory Concentration) that were under 6.3 µM [33] (Figure 1).

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

**Figure 1.** Isolated iminosugars 1–3 from Batzella sp.

2.2. Bicyclic Guanidine Alkaloids

Eleven bicyclic guanidine metabolites including five bearing crambescin type A (4–8), three bearing crambescin type B (9–11) and further three possessing crambescin type C (12–14)
were recorded from the Mediterranean sponge *Crambe crambe*. Their structures were established using NMR and careful HRMS/MS data analyses for the complete assignment of the alkyl chain lengths. These compounds demonstrated cytotoxic activity against neuronal cell lines in micromolar range [34,40,41]. Additional homologue crambescin A (15), the only known bicyclic compound reported from the Caribbean sponge *Batzella* sp. Compound 15 displayed potent cytotoxicity against proliferating Vero cells and HIV gp120-human CD4 binding inhibition activity with IC$_{50}$ > 100 μM [14]. Further bicyclic compounds including dehydrocrambine A (16) recorded from *Monanchora* sp. that inhibits HIV-1 fusion [42]. Monanchorin (17), a guanidine alkaloid with unusual bicyclic skeleton from *Monanchora unigulata* showed very weak cytotoxic activity with IC$_{50}$ = 11.3 μM against IC2 murine mast cell lines [35]. The simple pyrimidine monalidine A (18), an anti-parasitic bicyclic guanidine alkaloid, was recently recorded from *Monanchora arbuscula* [43]. Urupocidins A (19) and B (20), bisguanidine alkaloids possessing unusual N-alkyl-N-hydroxyguanidine motif, were isolated from *Monanchora pulchra*. Urupocidin A (19) increases nitric oxide production in murine macrophages via inducing iNOS expression [44]. Recently, seven cytotoxic guanidine alkaloids were described from a French Polynesian *Monanchora* n. sp. including three bicyclic architectures possessing a free carboxylic acid group monanchoradins A–C (21–23) and four bicyclic compounds bearing crambescin A2 type skeleton with a short butyl-guanidine side chain including dehydrocrambescin A2 418 (24), (−)-crambescin A2 392 (25), (−)-crambescin A2 406 (26) and (−)-crambescin A2 420 (27) along with monalidine A (18). Most of these compounds showed antiproliferative and cytotoxic activities against several cancer cell lines including KB, HCT-116, HL-60, MRC-5 and B16-F10, with IC$_{50}$ values in the micromolar range. The bicyclic analogue monanchoradin A (21) that bearing a carboxylic acid functionality was found to be less potent, however, it is still in the nanomolar range. On the other hand, the bicyclic compounds 24–27 bearing the butyl-guanidine terminus were found more potent, in particular (−)-crambescin A2 420 (27) that was found to be the most active with IC$_{50}$ = 0.03 μM against KB cancer cell lines [39]. Moreover, the simple compound 18 showed potent antiproliferative and cytotoxic activities against KB, HCT-116, MDA-435, HL-60 and MRC-5 with an IC$_{50}$ values 0.2/0.4, 0.84/0.74, 0.32/0.86, 1.3/1.3, 0.55/0.60 μM respectively. It is worth noting that the bicyclic (−)-crambescin compounds 25–27 are enantiomers for the antipodal bicyclic (+)-crambescins, recently isolated from the marine sponge *Pseudaxinella reticulata* (now known as *Dragmacidon reticulatum*, family Axinellidae) and their recording draws important insights about chirality and its dependence on the species of sponge [45] (Figure 2).
2.3. Tricyclic Guanidine Alkaloids Bearing Ptilocaulin

Four tricyclic compounds including 8a,8b-dehydroptilocaulin (28), 8a,8b-dehydro-8-hydroxyptilocaulin (29), 1,8a,8b,3a-didehydro-8-hydroxyptilocaulin (30) and mirabilin B (31) were recorded from the Bahamas marine sponge, *Batzellia* sp. [46]. (+)-Ptilocaulin (32), an antimicrobial and cytotoxic tricyclic guanidine alkaloid, in addition to isoptilocaulin (33) and (+)-8-hydroxyptilocaulin (34), were obtained from *Monanchora arbuscula* [38,47]. Moreover, (+)-ptilocaulin (32), exhibited antimicrobial activity against an oxacillin-resistant strain of *Staphylococcus aureus* with IC$_{50}$ = 1.3 µM [48]. Further three tricyclic guanidine alkaloids, including 1, 8a; 8b, 3a-didehydro-8β-hydroxyptilocaulin (35), 1, 8a; 8b, 3a-didehydro-8α hydroxyptilocaulin (36) and mirabilin B (31), were described from *Monanchora unguifera* [49]. The mixture of 35 and 36 was active against the malaria parasite *Plasmodium falciparum* with an IC$_{50}$ = 3.8 µM. Furthermore, mirabilin B (31) exhibited antifungal activity against *Candida neoformans* with an IC$_{50}$ = 7.0 µM and antiprotozoal activity against *Leishmania donovani* with an IC$_{50}$ = 17 µM [49]. The tricyclic guanidines 31–36 were identified from a Brazilian specimen of *Monanchora arbuscula* and were tested for their cytotoxicity against four cancer cell lines including HL-60, MDA-MB-435, HCT-8 and SF-295. The two compounds (+)-ptilocaulin (32) and (+)-8-hydroxyptilocaulin (34) displayed cytotoxicity with IC$_{50}$ values ranging from 5.8–40.0 and 7.9–61.5 µM respectively. However, the other compounds 31, 35 and 36 exhibited no activity. Additionally, compounds 32 and 34 were tested for their hemolytic activity against potential damage of mouse erythrocytes plasma membrane, where they displayed effective concentrations with EC$_{50}$ values of 577.95 and 352.91 µM respectively [50]. Further anti-parasitic tricyclic guanidine alkaloid arbusculidine A (37) was reported recently from *Monanchora arbuscula* [43] (Figure 3).
2.4. Tricyclic Pyrroloquinoline Alkaloids

Seven highly functionalized pyrroloquinoline alkaloids including three compounds named batzellines A–C (38–40) and four compounds named isobatzellines A–D (41–44) were isolated from the deep-water Bahama’s sponge *Batzella* sp. The isobatzellines A–D (41–44) showed in vitro cytotoxicity against P388 leukemia cell with IC$_{50}$ values 0.42, 2.6, 12.6 and 20 µM and moderate antifungal activity against *Candida albicans* with IC$_{50}$ values of 3.1, 25, 50 and 25 µM respectively [55]. Further brominated compounds incorporating the pyrroloiminoquinone moiety, trivially named discorhabdins P, S, T and U (45–48) were obtained from a deep-water marine sponge of the genus *Batzella*. Discorhabdin P (45) inhibited CaN and CPP32 with IC$_{50}$ values of 0.55 and 0.37 µM respectively. It also showed in vitro cytotoxicity against the cultured murine P-388 tumor cell line and human lung carcinoma A-549 cell line, with IC$_{50}$ values of 0.025 and 0.41 µM, respectively [53]. Compounds 46–48 displayed in vitro cytotoxicity against cultured murine P-388 tumor cells, with IC$_{50}$ values of 3.08, >5 and 0.17 µM, respectively. Further cytotoxicity was also observed for A-549 human lung adenocarcinoma cells, with IC$_{50}$ values of >5, >5 and 0.17 µM and for PANC-1 human pancreatic cells with IC$_{50}$ values of 2.6, 0.7 and 0.069 µM, respectively [54]. A comprehensive review on their therapeutic applications has been reported [55]. Additionally, secobatzellines A–B (49–50), two simple pyrroloiminoquinone enzyme inhibitors were recorded from a deep-water marine sponge of the genus *Batzella*. Secobatzelline B (50) is an artifact compound that was obtained during the purification process. Secobatzelline A (49) inhibited calcineurin (CaN) and CPP32 with IC$_{50}$ values of 0.55 and 0.02 µM. Moreover, secobatzelline B (50) inhibited calcineurin (CaN) IC$_{50}$ values of 2.21 µM. Furthermore, compounds 49 and 50 displayed cytotoxicity in vitro against the cultured murine P-388 tumor cell line, with IC$_{50}$ values 0.06, 1.22 µM and against human lung carcinoma A-549 cell line, with IC$_{50}$ values of 0.04, 2.86 µM [56]. A huge number of synthetic aminooiminoquinone and aminooquinones analogues were prepared and tested as caspase inhibitors [57]. Furthermore, a comprehensive evaluation for the cytotoxic activity of compounds 38–39, 41–44 and 49–50 were determined against four different pancreatic cell lines Panc-1, AsPC-1, BxPC-3 and MIA-PaCa2 as well as in the Vero cell line, an epithelial cell line from the kidney tissue of an African green monkey [58] (Figure 4).
Batzelladines represent a distinct class of particular guanidine-derived alkaloids that usually contain two main guanidinic moieties. Chemically, they are esters compounds that bear a principle tricyclic ring system named clathriadic acid that acting as an acidic portion bonded to another clathriadic acid molecule or crambescin A bicyclic system as an alcoholic part. Such a unique class of marine alkaloids is assumed to be synthesized biomimetically from different modes of cyclization between a polyketide-derived chain and a putative guanidine precursor affording these structurally complex metabolites [59]. These natural compounds are known for their potent bioactivities [13,14]. A considerable number of bioactive batzelladines were recorded from Batzella sponges. Batzelladines A–E (51–55), five potential inhibitors of HIV gp120-human CD4 binding were recorded from the Caribbean sponge Batzella sp. [13,14]. Batzelladines F–I (56–59), four inducers of p56lck-CD4 dissociation, were isolated from Batzella sp. collected from Jamaica [60]. Batzelladine J (60) was isolated from the Caribbean Monanchora unguifera [61]. A further six guanidines—including batzelladines K–N (61–64), batzelladine C (53) and dehydrobatzelladine C (65)—were discovered from Jamaican Monanchora unguifera with activities against several cancer cell lines, protozoa, HIV-1 and AIDS [14,62,63]. Batzelladine C (53) displayed anti-HIV-1 activity at an EC50 of 7.7 μM [63]. Four batzelladines 66–69 containing crambescin A bicyclic system in addition to dihomodehydrobatzelladine (70) were reported from the Caribbean Monanchora arbuscula. These compounds displayed mild antitumor activity with GI50 (3–7 μM) against three cancer cell lines, lung carcinoma A549, colon carcinoma HT-29 and breast MDA-MB-231, in addition to antimalarial activity against protozoa [64]. Norbatzelladine L (71) was isolated from unidentified species, Monanchora sp. that displayed MNTC (maximum non-toxic concentration) at 2.5 μg mL−1 against HSV-1, with 97% of inhibition in the viral adsorption phase. Furthermore, it displayed cytotoxicity against several human cancer cell lines including leukemia, colorectal, breast, melanoma and glioblastoma [65,66]. Two anti-infective tricyclic members with unique stereochemical features—named merobatzelladines A–B (72–73)—were isolated from Monanchora sp. Merobatzelladines A–B exhibited moderate antimicrobial activity against Vibrio anguillarum with inhibitory zones of 9–10 mm on application of 50 μg of a sample to a paper disk of 6 mm diameter.

Figure 4. Isolated pyrroloquinoline alkaloids 38–50 from Batzella sp.

2.5. Polycyclic Alkaloids Bearing Batzelladine

These compounds displayed mild antitumor activity with GI50 (3–7 μM) against three cancer cell lines, lung carcinoma A549, colon carcinoma HT-29 and breast MDA-MB-231, in addition to antimalarial activity against protozoa [64]. Norbatzelladine L (71) was isolated from unidentified species, Monanchora sp. that displayed MNTC (maximum non-toxic concentration) at 2.5 μg mL−1 against HSV-1, with 97% of inhibition in the viral adsorption phase. Furthermore, it displayed cytotoxicity against several human cancer cell lines including leukemia, colorectal, breast, melanoma and glioblastoma [65,66]. Two anti-infective tricyclic members with unique stereochemical features—named merobatzelladines A–B (72–73)—were isolated from Monanchora sp. Merobatzelladines A–B exhibited moderate antimicrobial activity against Vibrio anguillarum with inhibitory zones of 9–10 mm on application of 50 μg of a sample to a paper disk of 6 mm diameter.
Moreover, 72–73 also inhibited *Trypanosoma brucei* (GUT at 3.1) with IC$_{50}$ = 0.24 µg mL$^{-1}$ each. Furthermore, they display moderate inhibitory activity against the K1 strain of *Plasmodium falciparum* with an IC$_{50}$ = 0.48 µM and 0.97 µM, respectively [67]. Four anti-parasitic batzelladines (74–77) against *Trypanosoma cruzi* and *Leishmania infantum* were recently recorded from *Monanchora arbuscula* [43,68]. Numerous synthetic batzelladines and their derivatives showed potent activities against HIV-1 and AIDS opportunistic infectious pathogens, inhibition of HIV-1 envelope-mediated fusion [69], inhibitors of HIV-1 Nef interactions with p53, actin and p56lck [70], antimalarial, antileishmanial, antimicrobial and antiviral (HIV-1) activities [71], inhibitors against HIV-1 reverse transcriptase (RT) [72] and antileishmanial [73] (Figures 5 and 6).

Figure 5. Isolated batzelladine alkaloids 51–64.
2.6. Pentacyclic Alkaloids Bearing Crambescidin

Crambescidines are pentacyclic guanidine-derived alkaloids that represent recognizable complex marine metabolites. Chemically, they bear a common core of (5,6,8b)-triazaperhydroacenaphthalene in their molecules (trivially named as vessel) that coupled with a linear ω-hydroxy fatty acid (spermidine or hydroxyspermidine). These compounds vary from one to another in the length of the internal polymethylene chain and the oxidation degree of the two-spiro rings within the pentacyclic core. This group of compounds covers the major secondary metabolites recorded from these three genera. Since the discovery of the parent antiviral and cytotoxic marine metabolite ptilomycalin A (78) by Kashman and co-workers [74] from Ptilocaulis spiculifer (family Axinellidae) and Hemimycale sp. (family Hymedesmiidae) collected from the Red Sea coast in 1989, renewable efforts led to the discovery of further crambescidin analogues. Crambescidin 800 (79), crambescidin 816 (80), crambescidin 830 (81) and crambescidin 844 (82) were recorded from the Mediterranean marine sponge Crambe crambe [75]. These compounds demonstrated antiviral and cytotoxic activity against Herpes simplex virus, type1 (HSV-1) and cytotoxic activity against L1210 murine leukemia cells. Compounds 79, 80 and 82 showed complete inhibition for HSV-1 and 98% of L1210 cell growth at concentration of IC50 = 0.1 μM. Furthermore, crambescidin 816 (80) displayed potent Ca2+ antagonist activity and inhibited the acetylcholine-induced contraction of guinea pig ileum within very low concentrations [17], however, recent novel evidence showed that compound 80 partially blocked CaV
and NaV channels in neurons, proposes that this compound might be included in decreasing the neurotransmitter release and synaptic transmission within the central nervous system [76]. Further, recent study proved that crambescidin 816 (80) could be stored into specialized sponge cells where it can be dispersed into the water affording a chemical umbrella surrounding the Crambe crambe sponge [77]. Recently, Botana and co-workers [78] reported important insights about the mechanism of the neurons cytotoxic activity of crambescidin 816 (80) in primary cultures of cortical neurons. These results showed that compound 80 is responsible for the decreasing of neuronal viability and hence provided a dose-dependent increase in cytosolic Ca\(^{2+}\) level that was also linked to the presence of Ca\(^{2+}\) in the extracellular media. Crambescidins 78, 79 and 80 were recorded also from Batzella sp. [14]. 13,14,15-isocrambescidin 800 (83) with trans-ring junction within the pentacyclic core and crambidine (84) were discovered from Crambe crambe [17,79]. Surprisingly, compound 83 was found to be a less potent cytotoxic against L1210 cells compared to other crambescidines and there was no observed antiviral activity against HSV-1. This observation could be attributed to the enclosed ionic pocket feature found in 78 and related crambescidins and lacking in 83 [80]. Additional crambescidin analogues with a chlorinated spermidine motif including crambescidin 818 (85), crambescidin 834 (86), crambescidin 673 (87), crambescidin 687 (88) and 13,14,15-isocrambescidin 657 (89) without a spermidine unit were recorded from the FABMS guided isolation of Crambe crambe extracts. The ADMET predictor revealed that ptilomycalin and crambescidin 800 (78–79) possess three features of the Lipinski guidelines. Additionally, 78 showed low flexibility and a low tendency to permeate into cell membranes. However, compound 79 displayed low permeability, low flexibility and less tendency to permeate the cell membranes [81] Compounds 87, 88 and 89 exhibited in vitro cytotoxicity against L1210 murine leukemia five times compared to compound 80. Furthermore, they displayed antimicrobial activity against Rhodotorula glutinis [82,83]. Crambescidin 800 (79), crambescidin 359 (90) and crambescidin 431 (91) have been isolated from Monanchora unguiculata [62]. Crambescidin 826 (92) and fromiamycalin (93) were recorded from Monanchora sp. They inhibited HIV-1 envelope-mediated fusion in vitro with an IC\(_{50}\)’s = 1–3 \(\mu\)M [14,42]. Indeed 78, 79 and 93 displayed high cytotoxic activity against CEM 4 infected by HIV-1 with CC-50 of 0.11 \(\mu\)g mL\(^{-1}\), without cytoprotective effects, at a dose of <0.1 \(\mu\)M [84]. The antifungal 78 inhibits melanogenesis of Cryptococcus neoformans in vitro through the inhibition of the biosynthesis of laccase in the melanin biosynthetic pathway with an IC\(_{50}\) value of 7.3 \(\mu\)M [85]. Additionally, 79 induced a morphological change with neurite outgrowth in neuro 2A cells at concentration of 0.03–0.1 \(\mu\)M and recorded to induce the differentiation of K562 chronic myelogenous leukemia (CML) cells into erythroblasts accompanied by cell cycle arrest at the S-phase as well [86]. Further pentacyclic members were described, including crambescidin acid (94) from Monanchora unguiculata [35] and crambescid acid (95) from Monanchora unguifera [61]. Crambescidin 359 (90) and 16-\(\beta\)-hydroxycrambescidin 359 (96) were obtained from Monanchora unguifera [63]. Ptilomycalin D (97) showed cytotoxicity against cancer cell line P-388 with IC\(_{50}\) = 0.1 \(\mu\)M in addition to 78 and 95 were reported from Monanchora dichandra [36]. Monanchocidins A–E (98–102) are five unusual pentacyclic guanidine alkaloids with a morpholine modified spermidine motif from Monanchora pulchra. These compounds exhibited potent cytotoxic activities against HL-60 human leukemia cells with IC\(_{50}\) values of 540, 200, 110, 830 and 650 \(\mu\)M respectively [37]. Monanchocidin A (97) showed anti-migratory activity against several human cancer cell lines where it is able to prevent local expansion and metastatic spread of cancer cells [87]. Moreover, it could be a promising new compound for overcoming resistance to standard therapies in genitourinary malignancies by the induction of autophagy and lysosomal membrane permeabilization [88]. Monanchocidins A–B (103–104), two pentacyclic with a modified spiro five-membered ring, showed potent cytotoxicity against HL-60 human leukemia cells with the IC\(_{50}\) values 120 and 140 nM, respectively, were isolated from Monanchora pulchra [89]. Recently, compound 104 was recorded to inhibit of the TRPV1, TRPV2 and TRPV3 channels with EC\(_{50}\) values 6.02, 2.84 and 3.25 \(\mu\)M, respectively, however it displayed no activity against the TRPA1 receptor [90]. Moreover, monanchomycalin C (105) exhibited cytotoxicity against human breast cancer cell lines.
MAD-MB-231 with an IC50 of 8.2 µM, isolated from Monanchora pulchra [91]. Normonanchocidins A–B and D (106–108) were isolated from Monanchora pulchra. Compound 106 and a mixture of 107 and 108 (1:1) displayed cytotoxic activities against human leukemia THP-1 cells with IC50 values of 2.1 µM and 3.7 µM and against cervix epithelial carcinoma HeLa cells with IC50 of 3.8 µM and 6.8 µM, respectively [92]. Recently, further three cytotoxic pentacyclic guanidine compounds including crambescin 786 (109), crambescin 814 (110) and 20-norcrambescidic acid (111) along with pentacyclic analogues 79, 90, 92 and 95 were isolated from a French Polynesian sponge Monanchora n. sp. The isolated compounds showed potent antiproliferative and cytotoxic activities against KB, HCT-116, HL-60, MRC-5 and B16-F10 cancer cells. Compounds 109, 110 and 111 exhibited cytotoxicity against KB cell lines with an IC50 values 0.3 µM, 5 nM and 0.5 µM, respectively. The two crambescidin 95 and 111 where the (anchor) motif is terminated with the carboxylic acid functionality displayed potent cytotoxic activity against KB cell lines with IC50 = 0.55 µM, however, they still less active compared with analogues possessing spermidine terminus. Furthermore, crambescidin 800 (79) exhibited the highest cytotoxic activity, while shorter pentacyclic homologue 109 along with the longer one 110 were found less active. These observations might highlight the impact of the polymethylene chain length within the (anchor) motif as a spacer for two site interactions. Crambescidin 359 (90), possessing only a pentacyclic core, showed no activity against KB cell lines and this correlates with the importance of the spermidine part for cytotoxicity. Regarding the B16-F10 murine melanoma cells, crambescidins 79, 92 and 110 exhibited moderate activity with IC50 values of 0.2, 0.8 and 0.2 µM respectively. The discovery of 20-norcrambescidic acid (111) with this new pentacyclic motif carries some biogenesis impacts and raises some important insights about the variation in the oxidation degree and the mode of cyclization within the pentacyclic core [39]. A further two new hybrid pentacyclic guanidines monanchoxymycalin A–B (112–113) were obtained from the Far-Eastern marine sponge Monanchora pulchra. They displayed cytotoxic activities against cervical epithelioid carcinoma HeLa cells and breast adenocarcinoma MDA-MB231 cells [93]. Additionally, ptilomycalins E–H (114–117)—with guanidinic modified spermidine—were recorded from the Madagascar marine sponge Monanchora unguiculata. They displayed promising antimalarial activity against Plasmodium falciparum with IC50 values 0.38, 0.30 and 0.27 µM respectively [94,95] (Figures 7 and 8).

Figure 7. Isolated pentacyclic crambescidin alkaloids 78–89.
Figure 8. Isolated pentacyclic crambescidin alkaloids 90–117.
2.7. Acyclic Guanidine Alkaloids

Small number of open chain guanidine-derived alkaloids was recorded. Pulchranin A (118), was described as the first marine non-peptide inhibitor of TRPV-1 channels with an EC\textsubscript{50} value 41.2 µM, in addition two other acyclic members pulchranins B–C (119–120) reported from the Far-Eastern marine sponge Monanchora pulchra. Compounds 119 and 120 exhibited moderate inhibition against TRPV1 with EC\textsubscript{50} value 95 and 183 µM respectively and were even less potent against TRPV3 and TRPA1 receptors [96,97]. Moreover, two synthetic derivatives—dihydropulchranin A (121) and hexadecylguanidine (122)—were prepared and studied for their TRPV channel-regulating activities. Compound 121 showed activity as an inhibitor of rTRPV1 and hTRPV3 receptors with EC\textsubscript{50} values of 24.3 and 59.1 µM, respectively, while compound 122 was found not active against those receptors [98]. Additionally, recent studies revealed that pulchranin A (118) exhibited cytotoxic properties and prevented EGF-induced neoplastic transformation in vitro [99]. Further, acyclic analogue unguiculin A (123) with a modified bis-guanidine spermidine motif was isolated from the Madagascar marine sponge Monanchora unguiculata. It displayed antimalarial activity against the parasite Plasmodium falciparum with IC\textsubscript{50} value of 6.04 µM [94,95]. Recently, a further two acyclic bis-guanidine alkaloids—named unguiculins B–C (124–125), beside unguiculin A (123)—were discovered from the French Polynesian Monanchora n. sp. sponge. These compounds displayed potent cytotoxic activity against KB cell lines with IC\textsubscript{50} values 0.19/0.22, 0.08/0.09 and 0.03/0.03 µM respectively. Such activity might be attributed to the two terminal guanidines ends. Moreover, unguiculin C (125), the shorter homologue was found the most active. This could be concluded of how the chain and its length can play an important role as a spacer between two sites of interaction. Moreover, unguiculin B (124) showed further cytotoxicity against HCT-116, HL-60 and MRC-5 cell lines with IC\textsubscript{50} values 3.6/3.6, >10/>10 and 9.6/11.4 µM respectively [100,101] (Figure 9).

2.8. Terpenoid Compounds

Marine sponges belong to Monanchora genus have also produced a small number of terpenoid metabolites and classical sterols [102]. Nine sesterterpenoids 126–134 were isolated from the Korean Monanchora sp. along with four phorbaketales 135–138. These compounds were investigated for their cytotoxic activity against four human cancer cell lines—A498, ACHN, MIA-paca and PANC-1—where some of them showed potent cytotoxicity [103]. Seven cytotoxic 5α,8α-epidioxy sterols 139–145 were also described from Monanchora sp. These sterols showed moderate cytotoxicity against several human carcinoma cell lines including renal (A-498), pancreatic (PANC-1 and MIAPaCa-2) and colorectal (HCY-116) cancer cell lines [104]. Monanchosterols A–B (146–147) were identified from a South Korean Monanchora sp. and described as the first examples of naturally occurring steroids bearing a rearranged...
bicyclo [4.3.1] A/B ring system. Moreover, Monanchosterols A–B (146–147) exhibited significant inhibition of mRNA expression of IL-60 without notable cytotoxicity to the cells in a dose-dependent manner [105] (Figure 10).

**Figure 10.** Isolated terpenoid and steroidal metabolites 126–147 isolated from *Monanchora* sp.

3. Biomimetic Landmarks of Polycyclic Guanidinium Motifs

The bio-mechanistic studies along with the structural analyses for the different polycyclic guanidine alkaloids revealed two important insights; the first is chemical; where they are sharing the same biogenesis routs. A second is ecological; where marine sponges that produced such metabolites could be systematically classified under the same order. Generally, the different polycyclic guanidinic moieties could be biomimetically synthesized by way of the double aza Michael strategy, by the addition of free guanidine to α, β unsaturated polyketide chains (Figure 11) [59].
3.1. Bicyclic Compounds Possessing Crambescins Type A, B and C

Snider and his team had several contributions towards the biomimetic synthesis of the polycyclic guanidinic motifs. The bicyclic crambescin alkaloids possess three different cyclic moieties—crambescin type A with tetrahydropyrrolo [1,2-c] pyrimidine nucleus, crambescin type B possesses an oxa-6,8-diazaspiro [4.5] motif, while crambescin type C displays a tetrahydropyrimidin fragment. Crambescins type B and C were isolated exclusively from the Mediterranean marine sponge *Crambe crambe* [34,40,41]. A postulated strategy showed that these three guanidinium cores could be constructed biomimetically through a conjugated Michael addition of guanidine to enone ester. This strategy seems pertinent since it gathers the formation of three different atom arrangements from one unified precursor (Figure 12) [106].

![Figure 11. Structural analysis of different polycyclic guanidine alkaloids.](image1)

![Figure 12. Proposed retrosynthetic analysis of the bicyclic alkaloids.](image2)
The less basic O-methylisourea was chosen as guanidine precursor instead of free guanidines. The condensation of O-methylisourea with previously prepared enone (148) followed by acid hydrolysis and desilylation afforded the corresponding dihydropyrimidine intermediate (149). In presence of methanolic ammonium acetate saturated with ammonia, 150 afforded the key compound 150, corresponding to crambescin type C. Subsequently, 150 was transformed to compound 151, corresponding to crambescin type A by mesylation, hydrogenolysis and cyclization. Compound 152 possesses crambescin type B was obtained by cyclization of 150 under basic condition (Figure 13) [106].

**Figure 13.** a: 2 equiv. O-methylisourea and 7 equiv. NaHCO₃ in DMF for 12 h at 60 °C, 79%; b: hydrolysis, TBAF, THF, 12 h, rt, 90%; c: NH₄OAc (1.5 equiv.), MeOH saturated with NH₃ at 60 °C for 2 days, 61%; d: MsCl, Et₃N in DCM for 30 min, 0 °C, 6 h, rt; e: Et₃N in CHCl₃, reflux, 12 h, 90%; f: Et₃N in CHCl₃, Δ, 12 h.

Based on the previous biomimetic approach, Berlinck and co-workers [43] accomplished the biomimetic synthesis of the cytotoxic and anti-parasitic monalidine A (18). 1,3-diketone 153 was introduced for condensation with guanidine free base to afford the corresponding pyrimidine 154 in 25% yield. Subsequently, the key intermediate 152 was cyclized using the Mitsunobu modified protocol to afford 18 as hydrochloride salt in a 67% yield (Figure 14).

**Figure 14.** a: Guanidine hydrochloride, t-BuOK, CF₃CH₂OH, 30 min, then 154, rt, 48 h, 25%; b: Ph₃P, imidazole, I₂, CH₂Cl₂, −18 °C, 6 h, 67%.

### 3.2. Tricyclic Possessing Ptilocaulin/Batzelladine

(±)-Ptilocaulin (32) was first synthesized biomimetically as a racemic mixture via Michael addition strategy by addition of free guanidine to enone 155 followed by intramolecular enamine formation. (−)-Ptilocaulin (156) was formed as a kinetic product where the guanidine was added to the less hindered top convex face of enone 155, whereas (+)-ptilocaulin (32) was obtained as a thermodynamic adduct as the guanidine was added to the more hindered bottom side of enone 155. This strategy highlights and proves a unique unified biosynthetic route for ptilocaulins and related tricyclanic analogues (Figure 15) [107–109].
The tricyclic guanidinium framework of batzelladine K (61) was biomimetically synthesized through the addition of free guanidine to a bis-enone 157 affording the pyrrolidone-dione 158, which was subsequently introduced to cyclization followed by iminium ion formation giving rise to the full fused tricyclic guanidinium core. A subsequent reduction afforded 61. A unified synthetic strategy was applied to ptilocaulin (32), isoptiloaulin (33) and batzelladine K (61), which indicated that these classes of tricyclic guanidines are subjected to the same biomimetic gate (Figure 16) [71,110,111].

3.3. Pentacyclic Possessing Ptilomycalins, Crambescidins and Monanchomycalins

Numerous total syntheses of the pentacyclic guanidinium core of ptilomycalin A (78), crambescidin 800 (79) and crambescidin 359 (95) were biomimetically achieved [23,112,113]. A biomimetic synthesis of the methyl ester of the pentacyclic nucleus of 78 was conducted through a conjugated condensation of O-methylisourea as protected guanidine strategy with double Michael acceptor bis-enone 159 as α-β unsaturated polyketide framework. Subsequently, desilylation under acidic conditions provided the first seven-membered spiroaminal ring within the intermediate 160. Later, the second six-membered spiroaminal ring was achieved under basic conditions followed by subsequently aminal formation affording the ptilomycalin A pentacyclic framework 161 (vessel) in one single biomimetic step (Figure 17).
Recently, a detailed biomimetic gate was proposed illustrating the biogenesis of different pentacyclic guanidinium cores. The pentacyclic core of monanchomycalin A (103), suggests polyketide-like biogenesis, followed by spermidine-spermidine condensations. Two different precursors were employed, including either nine acetate units as in monanchomycalin B (104) and other known pentacyclic members, or ten acetate and one propionate units as in monanchomycalin A (103). To finish the pentacyclic guanidinium polyketide framework (vessel), a cyclization key-step developed by adding guanidine to bis-β, β unsaturated chain followed by imine-enamine tautomerization (transformation (a)). Further conversions including the allylic oxidation (transformation (b)) to afford putative intermediates (III and/or IV) followed by cyclization-elimination (c) and (d) to generate monanchomycalins A–B (103–104) and related pentacyclic analogues. Moreover, the interconversion of the presumptive intermediates III and IV (transformation (e)) through allylic rearrangement like reactions also might be possible (Figure 18) [89].

Recently, Guzzì and collaborators [96] proposed biogenetic correlations linking between the acyclic guanidine alkaloid pulchranin A (118) and the pentacyclic crambescidins and monanchomycalins.
A–B (103–104). This proposed biogenetic rout could unify the variation in the oxidation degree for the left-hand side spiroaminal rings (Figure 19).

![Figure 19. Pulchranin A (118), as a biosynthetic precursor for pentacyclic compounds (103–104).](image)

4. Conclusions

In conclusion, we have presented complete and comprehensive up-to-date literature survey exclusively dedicated to the chemistry, biology and insights on the most leading biomimetic syntheses of guanidine derived natural products isolated from marine sponges of three genera Batzella, Crambe and Monanchora. One hundred forty-seven marine natural products were recorded with distinct structural diversities that afforded wide scope of bioactivities. For their chemodiversity, along with their displayed biological potentialities, they still present promising and attractive marine species that are worth attracting the worldwide interest of natural products chemists and pharmacologists.

Acknowledgments: This work was supported by the mission sector of the Ministry of High Education of the Arab Republic of Egypt (Egyptian Cultural Bureau in Paris, France); Amr El-Demerdash’s was granted and completely funded. Many thanks to Ali Al-Mourabit and his research team at the ICSN-CNRS for hosting, supervising and supplying with research facilities.

Author Contributions: Amr El-Demerdash wrote the first draft of the manuscript. Atanas G. Atanasov, Anupam Bishayee, Mamdouh Abdel-Mogib, John N. A. Hooper and Ali Al-Mourabit critically revised and improved the manuscript. All the authors read and approved the final version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

- ADMET: absorption, distribution, metabolism and excretion–toxicity in pharmacokinetics
- EC50: Half maximal effective concentration
- GI50: Half maximal growth inhibition
- gp120: glycoprotein 120
- HIV-1: Human immunodeficiency virus 1
- HSV-1: Herpes simplex virus 1
- IC50: Half maximal inhibitory concentration
- MIC: Minimum inhibitory concentration

References

1. Montaser, R.; Luesch, H. Marine natural products: A new wave of drugs. Future Med. Chem. 2011, 3, 1475–1489. [CrossRef] [PubMed]
2. Martins, A.; Vieira, H.; Gaspar, H.; Santos, S. Marketed marine natural products in the pharmaceutical and cosmeceutical Industries: Tips for success. Mar. Drugs 2014, 12, 1066–1101. [CrossRef] [PubMed]
3. Rangel, M.; Falkenberg, M. An overview of the marine natural products in clinical trials and on the market. J. Coast. Life Med. 2015, 3, 421–428. [CrossRef]
4. Shanmugam, A.; Vairamani, S. Biologically active metabolites from sponges and their activities. In Marine Sponges: Chemico-biological and Biomedical Applications; Pallela, R., Ehrlich, H., Eds.; Springer: Berlin, Germany, 2016; pp. 115–142; ISBN 978-81-322-2794-6.
5. Sfecci, E.; Lacour, T.; Amad, P.; Mehiri, M. Polycyclic guanidine alkaloids from Poecilosclerida marine sponges. *Mar. Drugs* **2016**, *14*, 77. [CrossRef] [PubMed]

6. Berlinck, R.G.S. Some aspects of guanidine secondary metabolites. *Prog. Chem. Nat. Prod.* **1995**, *119–295*. [CrossRef]

7. Sun, H.H.; Sakemi, S.; Burres, N.; McCarthy, P. Isobatzellines A, B, C and D: cytotoxic and antifungal pyrroloquinoline alkaloids from the marine sponge *Batzella sp.* *J. Org. Chem.* **1990**, *55*, 4964–4966. [CrossRef]

8. Jares-Erijman, E.A.; Sakai, R.; Rinehart, K.L. Crambescidins: New antiviral and cytotoxic compounds from the sponge *Crambe crambe*. *J. Org. Chem.* **1991**, *6*, 5712–5715. [CrossRef]

9. Gochfeld, D.J.; El-Sayed, K.A.; Yousaf, M.; Hu, J.F.; Bartyzel, P.; Dunbar, D.C.; Wilkins, S.P.; Zjawiony, J.K.; Schinazi, R.F.; Schlueter, W.S.; et al. Marine natural products as lead anti-HIV agents. *Mini Rev. Med. Chem.* **2003**, *3*, 401–424. [CrossRef] [PubMed]

10. Zhou, X.; Liu, J.; Yang, B.; Lin, X.; Yang, X.; Liu, Y. Marine natural products with anti-HIV activities in the last decade. *Curr. Med. Chem.* **2013**, *20*, 953–973. [CrossRef] [PubMed]

11. Rubiolo, J.A.; López-Alonso, H.; Roel, M.; Vieytes, M.R.; Thomas, O.; Ternon, E.; Vega, F.V.; Botana, L.M. Mechanism of cytotoxic action of crambescidin-816 on human liver-derived tumour cells. *Br. J. Pharmacol.* **2014**, *171*, 1655–1667. [CrossRef] [PubMed]

12. Berlinck, R.G.S. Some aspects of guanidine secondary metabolites. *Stud. Nat. Prod. Chem.* **1995**, *1145–1173*. [CrossRef] [PubMed]

13. Mai, S.H.; Nagulapalli, V.K.; Patil, A.D.; Truneh, A.; Westley, J.W. Marine Compounds as HIV Inhibitors. U.S. Patent Application No. WO9301193 (A1), 21 January 1993.

14. Patil, A.D.; Kumar, N.V.; Kokke, W.; Bean, M.F.; Freyer, A.J.; Brosse, C.D.; Mai, S.; Truneh, A.; Faulkner, D.J.; Carte, B.; et al. Novel alkaloids from the sponge *Batzella sp.* Inhibitors of HIV gp120-Human CD4 Binding. *J. Org. Chem.* **1995**, *60*, 1182–1188. [CrossRef]

15. Nakao, Y.; Fusetani, N. Enzyme inhibitors from marine invertebrates. *J. Nat. Prod.* **2007**, *70*, 689–710. [CrossRef] [PubMed]

16. Carté, B.K. Marine natural products as a source of novel pharmacological agents. *Curr. Opin. Biotechnol.* **1993**, *4*, 275–279. [CrossRef]

17. Berlinck, R.G.S.; Braekman, J.C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. Polycyclic guanidine alkaloids from the marine sponge *Crambe crambe* and Ca²⁺ channel blocker activity of crambescidin 816. *J. Nat. Prod.* **1993**, *56*, 1007–1015. [CrossRef] [PubMed]

18. Rubiolo, J.A.; Ternon, E.; Lopez-Alonso, H.; Thomas, O.; Vega, F.V.; Vieytes, M.R.; Botana, L. Crambescidin-816 Acts as a fungicidal with more potency than crambescidin 800 and 830, Inducing cell cycle arrest, increased cell size and apoptosis in *Saccharomyces cerevisiae*. *Mar. Drugs* **2013**, *11*, 4419–4434. [CrossRef] [PubMed]

19. Amad, P.; Charroin, C.; Baby, C.; Vacelet, J. Antimicrobial activities of marine sponges from the Mediterranean Sea. *Mar. Biol.* **1987**, *94*, 271–275. [CrossRef]

20. Sun, X.; Sun, S.; Ference, C.; Zhu, W.; Zhou, N.; Zhang, Y.; Zhou, K. A potent antimicrobial compound isolated from *Clathria cervicornis*. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 67–69. [CrossRef] [PubMed]

21. Mishra, A.; Batra, S. Thiourea and guanidine derivatives as antimalarial and antimicrobial agents. *Curr. Med. Chem.* **2013**, *13*, 2011–2025. [CrossRef]

22. Shimokawa, J.; Ishiwata, T.; Shirai, K.; Koshibo, H.; Tananati, A.; Nakata, T.; Hashimoto, Y.; Nagasawa, K. Total synthesis of (+)-Batzelladine A; (-)-Batzelladine D and identification of their target protein. *Chem. Eur. J.* **2005**, *11*, 6878–6888. [CrossRef] [PubMed]

23. Moore, C.G.; Murphy, P.J.; Williams, H.L.; McGown, A.T.; Smith, N.K. Synthetic studies towards ptilomycalin A: Total synthesis of crambescidin 359. *Tetrahedron Lett.* **2007**, *63*, 11771–11780. [CrossRef]

24. Sekine, M.; Iijima, Y.; Iwamoto, O.; Nagasawa, K. Synthesis of (+)-Batzelladine K. *Heterocycles* **2010**, *80*, 395–408. [CrossRef]

25. Wierzej ska, J.; Ohshima, M.; Inuzuka, T.; Sengoku, T.; Takahashi, M.; Yoda, H. Total synthesis and absolute stereochemistry of (+)-batzellaside B; its C8-epimer, a new class of piperidine alkaloids from the sponge *Batzella sp.* *Tetrahedron Lett.* **2011**, *52*, 1173–1175. [CrossRef]

26. Babij, N.R.; Wolfe, J.P. Asymmetric total synthesis of (+)-Merobatzelladine B. *Angew. Chem. Int. Ed.* **2012**, *51*, 4128–4130. [CrossRef] [PubMed]

27. Ma, Y.; De, S.; Chen, C. Syntheses of cyclic guanidine-containing natural products. *Tetrahedron* **2015**, *71*, 1145–1173. [CrossRef] [PubMed]
28. Parr, B.T.; Economou, C.; Herzon, S.B.A. Concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials. *Nature* **2015**, *525*, 507–510. [CrossRef] [PubMed]

29. Van Soest, R.W.M.; Braekman, J.C.; Faulkner, D.J.; Hajdu, E.; Harper, M.K.; Vacelet, J. The genus *Batzella*: A chemosystematic problem. *Bull. Inst. R. Sci. Nat. Belg.* **1996**, *66*, 89–101.

30. World Porifera Database. 2017. Available online: http://www.marinespecies.org/porifera/porifera.php?p=taxdetails&id=168731 (accessed on 20 March 2017).

31. World Porifera Database. 2017. Available online: http://www.marinespecies.org/porifera/porifera.php?p=taxdetails&id=131931 (accessed on 20 March 2017).

32. World Porifera Database. 2017. Available online: http://www.marinespecies.org/porifera/porifera.php?p=taxdetails&id=169014 (accessed on 20 March 2017).

33. Segraves, N.L.; Crews, P.A. Madagascar sponge *Batzellastri sp.* as a source of alkylated iminosugars. *J. Nat. Prod.* **2005**, *68*, 118–121. [CrossRef] [PubMed]

34. Berlinck, R.G.S.; Braekman, J.C.; Daloze, D.; Bruno, I.; Riccio, R.; Rogeau, D.; Amade, P. Crambines C1 and C2: Two further cytotoxic guanidine alkaloids from the sponge *Crambe crambe*. *J. Nat. Prod.* **1992**, *55*, 528–532. [CrossRef] [PubMed]

35. Meragelman, K.M.; McKee, T.C.; McMahon, J.B. Monanchorin, a bicyclic alkaloid from the sponge *Monanchora arbuscula*. *J. Nat. Prod.* **2004**, *67*, 1165–1167. [CrossRef] [PubMed]

36. Bensemhoun, J.; Bombarda, I.; Aknin, M.; Vacelet, J.; Gaydou, E.M. Ptilomycalin D, a polycyclic guanidine alkaloid from the marine sponge *Monanchora dianchora*. *J. Nat. Prod.* **2007**, *70*, 2033–2035. [CrossRef] [PubMed]

37. Makarieva, T.N.; Tabakmaher, K.M.; Guzii, A.G.; Denisenko, V.A.; Dmitrenok, P.S.; Shubina, L.K.; Kuzmich, A.S.; Lee, H.S.; Stonik, V.A. Monanchocidins B–E: Polycyclic guanidine alkaloids with potent antileukemic activities from the sponge *Monanchora pulchra*. *J. Nat. Prod.* **2011**, *74*, 1952–1958. [CrossRef] [PubMed]

38. Tavares, R.; Daloze, D.; Braekman, J.C.; Hajdu, E.; van Soest, R.W.M. 8b-hydroxyptilocaulin, a new guanidine alkaloid from the sponge *Monanchora reticulata*. *Org. Lett.* **2014**, *16*, 2828–2835. [CrossRef]

39. Chang, L.C.; Whittaker, N.F.; Bewley, C.A. Crambescidin 826 and Dehydrocrambine A: New polycyclic guanidine alkaloids from the sponge *Crambe crambe*. *J. Nat. Prod.* **1995**, *58*, 1139–1142. [CrossRef]

40. Hooper, J.N.A.; Debitus, C.; Al-Mourabit, A. Cytotoxic guanidine alkaloids from a French Polynesian *Monanchora* sp. sponge. *J. Nat. Prod.* **2016**, *79*, 1929–1937. [CrossRef] [PubMed]

41. Patil, A.D.; Freyer, A.J.; Offen, P.; Bean, M.F.; Johnson, R.K. Three new tricyclic guanidine alkaloids from the Caribbean sponge *Ptilocaulis* sp. *Tetrahedron* **2012**, *68*, 3410–3414. [CrossRef] [PubMed]

42. Segraves, N.L.; Crews, P.A. Madagascar sponge *Batzellastri sp.* as a source of alkylated iminosugars. *J. Nat. Prod.* **2005**, *68*, 118–121. [CrossRef] [PubMed]

43. Patil, A.D.; Freyer, A.J.; Offen, P.; Bean, M.F.; Johnson, R.K. Three new tricyclic guanidine alkaloids from the Caribbean sponge *Ptilocaulis* sp. *Tetrahedron* **2012**, *68*, 3410–3414. [CrossRef] [PubMed]

44. Kossuga, M.H.; Delira, S.P.; Nascimento, A.M.; Gambardella, M.T.P.; Berlinck, R.G.S.; Torres, Y.R.; Nascimento, G.G.F.; Pimenta, E.F.; Silva, M.; Thiemann, O.H.; et al. Isolation and biological activities from the sponge *Pseudaxinella reticulata*. *Org. Lett.* **2014**, *16*, 4292–4295. [CrossRef] [PubMed]

45. Jamison, M.T.; Molinski, T.F. Antipodal crambescin A2 homologues from the marine sponge *Pseudaxinella reticulata*. Antifungal structure–activity relationships. *J. Nat. Prod.* **2015**, *78*, 557–561. [CrossRef] [PubMed]

46. Estrada, P.; Freyer, A.J.; Offen, P.; Bean, M.F.; Johnson, R.K. Three new tricyclic guanidine alkaloids from the Caribbean sponge *Ptilocaulis* sp. *J. Nat. Prod.* **2015**, *78*, 74, 528–532. [CrossRef] [PubMed]
of secondary metabolites from the sponges *Monanchora aff. arbuscula*, *Aplysina* sp. *Petromica ciotalyptoides* and *Topsentia ophiraphidies*, from the ascidian *Didemnum ligulatum* and from the octocoral *Carijoa riisei*. *Quim. Nova* 2007, 30, 1194–1202. [CrossRef]

49. Hua, H.M.; Peng, J.; Fromczek, F.R.; Kelly, M.; Hamann, M.T. Crystallographic and NMR studies of antifreeze tricyclic guanidine alkaloids from the sponge *Monanchora unguifera*. *Bioorg. Med. Chem.* 2004, 12, 6461–6464. [CrossRef] [PubMed]

50. Ferreira, E.G.; Wilke, D.V.; Jimenez, P.C.; De oliveira, J.R.; Pessoa, O.D.L.; Silveria, E.R.; Viana, F.A.; Pessoa, C.; Maraes, M.O.; Hajdu, E.; et al. Guanidine alkaloids from *Monanchora arbuscula*: Chemistry and antitumor potential. *Chem. Biodivers.* 2011, 8, 1433–1445. [CrossRef]

51. Sakemi, S.; Sun, H.H.; Jefford, C.W.; Bemardinelli, G. Batzellines A, B and C. Novel pyrroloquinoline alkaloids from the sponge *Batolla* sp. *Tetrahedron Lett.* 1989, 30, 2517–2520. [CrossRef]

52. Sun, H.H.; Sakemi, S.I. Pyrroloquinoline Alkaloids, Batzellines and Isobatzellines from Marine Sponge and Methods of Use. U.S. Patent Application No. US5028613 (A), 2 July 1991.

53. Gunasekera, S.P.; McCarthy, P.J.; Longley, R.E.; Wright, A.E.; Lobkovsky, E.; Clardy, J. Discorhabdin P, a new enzyme inhibitor from a deep-water Caribbean sponge of the genus *Batzella*. *J. Nat. Prod.* 1999, 62, 173–175. [CrossRef] [PubMed]

54. Gunasekera, S.P.; Zuleta, I.A.; Longley, R.E.; Pomponi, S.A.; Wright, A.E. Aminoiminoquinone and Aminoquinine Alkaloid Compounds as Caspase Inhibitors. U.S. Patent No. WO2000002858 (A1), 20 January 2000.

55. Guzman, E.A.; Johnson, J.D.; Carrier, M.K.; Meyer, C.I.; Pitts, T.P.; Gunasekera, S.P.; Wright, A.E. Selective cytotoxic pyrroloiminoquinones from a deep-water Caribbean sponge of the genus *Batzella*. *J. Nat. Prod.* 1999, 62, 1208–1211. [CrossRef] [PubMed]

56. Guzman, E.A.; Johnson, J.D.; Carrier, M.K.; Meyer, C.I.; Pitts, T.P.; Gunasekera, S.P.; Wright, A.E. Selective cytotoxic activity of the marine-derived batzelladine compounds against pancreatic cancer cell lines. *Anti-Cancer Drugs* 2009, 20, 149–155. [CrossRef] [PubMed]

57. Capon, R.J.; Miller, M.; Rooney, F. Clathrins A–C: Metabolites from a southern Australian marine sponge *Clathria* species. *J. Nat. Prod.* 2001, 64, 643–644. [CrossRef] [PubMed]

58. Patil, A.D.; Freyer, A.J.; Taylor, P.B.; Cart, M.O.; Hajdu, E.; Zuber, G.; Johnson, R.K.; Faulkner, D.J. Batzelladines F–I, novel alkaloids from the sponge *Batzella* sp.: Inducers of p56lck-CD4 dissociation. *J. Org. Chem.* 2000, 65, 1615–1617. [CrossRef] [PubMed]

59. Hua, H.M.; Peng, J.; Fronczek, F.R.; Kelly, M.; Hamann, M.T. Crystallographic and NMR studies of enzyme inhibitors from a deep-water Caribbean sponge of the genus *Batzella*. *J. Nat. Prod.* 1999, 62, 193–196. [CrossRef] [PubMed]

60. Capon, R.J.; Miller, M.; Rooney, F. Clathrins A–C: Metabolites from a southern Australian marine sponge *Clathria* species. *J. Nat. Prod.* 2001, 64, 643–644. [CrossRef] [PubMed]

61. Gallimore, W.A.; Kelly, M.; Scheuer, P.J. Alkaloids from the sponge *Monanchora unguifera*. *J. Nat. Prod.* 2005, 68, 1420–1423. [CrossRef] [PubMed]

62. Braekman, J.C.; Daloze, D.; Tavares, R.; Hajdu, E.; van Soest, R.W.M. Novel polycyclic guanidine alkaloids from two marine sponges of the genus *Monanchora*. *J. Nat. Prod.* 2000, 63, 193–196. [CrossRef] [PubMed]

63. Hua, H.M.; Peng, J.; Dunber, D.C.; Schinazi, R.F.; Andrews, A.G.C.; Cuevas, C.; Fernandez, L.F.G.; Kelly, M.; Hamann, M.T. Batzelladine alkaloids from the Caribbean sponge *Monanchora unguifera* and the significant activities against HIV-1 and AIDS opportunistic infectious pathogens. *Tetrahedron* 2007, 63, 11179–11188. [CrossRef]

64. Hua, H.M.; Peng, J.; Dunber, D.C.; Schinazi, R.F.; Andrews, A.G.C.; Cuevas, C.; Fernandez, L.F.G.; Kelly, M.; Hamann, M.T. Batzelladine alkaloids from the Caribbean sponge *Monanchora unguifera* and the significant activities against HIV-1 and AIDS opportunistic infectious pathogens. *Tetrahedron* 2007, 63, 11179–11188. [CrossRef]

65. Galvão, M.O.; Hajdu, E.; et al. Guanidine alkaloids from *Monanchora unguifera* antiinfective tricyclic guanidine alkaloids from the sponge *Monanchora* sp. *Tetrahedron* 1987, 43, 303–306. [CrossRef]

66. Pessoa, C.; dos Santos, M.F.C.; Berlinsck, R.G.S.; Ferreira, P.M.P.; Cavalcanti, B.C. Cytotoxic batzelladine L from the Brazilian marine sponge *Monanchora arbuscula*. *Planta Med.* 2013, 79, PK6. [CrossRef]

67. Takishima, S.; Ishiyama, A.; Iwatsuki, M.; Otoguro, K.; Yamada, H.; Omura, S.; Kobayashi, K.; Van Soest, R.W.M.; Matsunaga, S. Merobatzelladines A and B, anti-infective tricyclic guanidines from a marine sponge *Monanchora* sp. *Org. Lett.* 2009, 11, 2655–2658. [CrossRef] [PubMed]
68. Martins, L.F.; Mesquita, J.T.; Pinto, E.G.; Thais, A.; Costa-Silva, T.A.; Borborema, S.E.T.; Junior, A.J.G.; Neves, B.J.; Andrade, C.H.; Al Shuaib, Z.; et al. Analogues of marine guanidine alkaloids are in vitro effective against *Trypanosoma cruzi* and selectively eliminate *Leishmania* (L.) *infantum* Intracellular amastigotes. *J. Nat. Prod.* 2016, 79, 2202–2210. [CrossRef] [PubMed]

69. Bewley, C.A.; Ray, S.; Cohen, F.; Collins, S.K.; Overman, L.E. Inhibition of HIV-1 envelope-mediated fusion by synthetic batzelladine analogues. *J. Nat. Prod.* 2004, 67, 1319–1324. [CrossRef] [PubMed]

70. Olszewski, A.; Sato, K.; Aron, Z.D.; Cohen, F.; Harris, A.; McDougall, B.R.; Robinson, W.E.; Overman, L.E.; Weiss, G.A. Guanidine alkaloid analogues as inhibitors of HIV-1 Nef interactions with p53, actin and p56lck. *Proc. Natl. Acad. Sci. USA* 2004, 101, 14079–14084. [CrossRef] [PubMed]

71. Ahmed, N.; Brahmbhatt, K.G.; Khan, S.I.; Jacob, M.; Tekwani, B.L.; Sabde, S.; Mitra, D.; Singh, I.; Khan, I.A.; Bhutani, K.K. Synthesis and biological evaluation of tricyclic guanidine analogues of batzelladline K for antimalarial, antileishmanial, antibacterial, antifungal and anti-HIV activities. *Chem. Biol. Drug Des.* 2013, 81, 491–498. [CrossRef] [PubMed]

72. Bennett, E.L.; Black, G.P.; Browne, P.; Hizi, A.; Jaffar, M.; Leyland, J.P.; Martin, C.; Oz-Gleenberg, I.; Murphy, P.J.; Roberts, T.D.; et al. Synthesis and biological activity of analogues of batzelladline F. *Tetrahedron* 2013, 69, 3061–3066. [CrossRef]

73. Tempone, A.G.; Martins, L.F.; Pinto, E.G.; Mesquita, J.T.; Bennett, E.L.; Black, G.P.; Murphy, P.J. Synthetic marine guanidines are effective antileishmanial compounds by altering the plasma membrane permeability. *Planta Med.* 2014, 80, P1154. [CrossRef]

74. Kashyan, Y.; Hirsh, S.; McConnell, O.J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. Ptilomycalin A: A novel polycyclic guanidine alkaloid of marine origin. *J. Am. Chem. Soc.* 1989, 111, 8925–8926. [CrossRef]

75. Rinehart, K.L.; Jares-Erijman, E.A. Crambescidins: New Antiviral and Cytotoxic Compounds from the Sponge *Crambe crambe*. U.S. Patent Application No. 5756734 (A), 26 May 1998.

76. Martin, V.; Vale, C.; Bondu, S.; Thomas, O.P.; Viytes, M.R.; Botana, L.M. Differential effects of crambescins and crambecidin 816 in voltage-gated sodium, potassium and calcium channels in neurons. *Chem. Res. Toxicol.* 2013, 26, 169–178. [CrossRef] [PubMed]

77. Ternon, E.; Zarate, L.; Chenesseau, S.; Croué, J.; Dumollard, R.; Marcelino, T.; Suzuki, M.T.; Thomas, O.P. Spheralization as a process for the exudation of chemical cues by the encrusting sponge *Crambe crambe*. *Sci. Rep.* 2016, 6, 29474. [CrossRef] [PubMed]

78. Mendez, A.G.; Juncai, B.; Silva, S.B.L.; Thomas, O.P.; Vázquez, V.M.; Alfonso, A.; Viytes, M.R.; Vale, C.; Botana, L.M. The marine guanidine alkaloid crambecidin 816 induces calcium influx and cytotoxicity in primary cultures of cortical neurons through glutamate receptors. *ACS Chem. Neurosci.* 2017, 8, 1608–1617. [CrossRef] [PubMed]

79. Jares-Erijman, E.A.; Ingrum, A.L.; Carney, J.R.; Rinehart, K.L.; Sakai, R. Polycyclic guanidine-containing compounds from the Mediterranean sponge *Crambe crambe*: The structure of 13,14,15-isocrambescidin 800 and the absolute stereochemistry of the pentacyclic guanidine moieties of the crambecidins. *J. Org. Chem.* 1993, 58, 4805–4808. [CrossRef]

80. Heys, L.; Moore, C.G.; Murphy, P.J. The guanidine metabolites of *Ptilocaulis spiculifer* and related compounds; isolation and synthesis. *Chem. Soc. Rev.* 2000, 29, 57–67. [CrossRef]

81. Gogineni, V.; Schinazi, R.F.; Hamann, M.T. Role of marine natural products in the genesis of antiviral agents. *Chem. Rev.* 2015, 115, 9655–9705. [CrossRef] [PubMed]

82. Shi, J.G.; Sun, F.; Rinehart, K.L. Crambescidin Compounds. U.S. Patent Application No. WO2013/01542 (A), 22 October 1998.

83. Rinehart, K.L.; Shi, J.G.; Sun, F. Crambescidin Compounds. U.S. Patent Application No. US2006028077 (A), 22 February 2000.

84. Palagiano, E.; De Marino, S.; Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carre, J.; Deitus, C.; Lucarain, L.; Provost, J. Ptilomycalin A, crambecidin 800 and related new highly cytotoxic guanidine alkaloids from the starfishes *Fromia monilis* and *Celerina heffernani*. *Tetrahedron* 1995, 51, 3675–3682. [CrossRef]

85. Dalsay, D.S.; Saludes, J.P.; Molinski, T.F. Ptilomycalin A inhibits laccase and melanization in *Cryptococcus neoformans*. *Bioorg. Med. Chem.* 2011, 19, 6654–6657. [CrossRef] [PubMed]

86. Aoki, S.; Kong, D.; Matsu, K.; Kobayashi, M. Erythroid differentiation in K562 chronic myelogenous cells induced by crambecidin 800, a pentacyclic guanidine alkaloid. *Anticancer Res.* 2004, 24, 2325–2330. [PubMed]
87. Dyshlovoy, S.A.; Venz, S.; Hauschild, J.; Tabakmakher, K.M.; Otte, K.; Madanchi, R.; Walther, R.; Guzii, A.G.; Makarieva, T.N.; Shubina, L.K.; et al. Anti-migratory activity of marine alkaloid monanchocidin A, proteomics-based discovery and confirmation. *Proteomics* 2016, 16, 1590–1603. [CrossRef] [PubMed]

88. Dyshlovoy, S.A.; Hauschild, J.; Amann, K.; Tabakmakher, K.M.; Venz, S.; Walther, R.; Guzii, A.G.; Makarieva, T.N.; Shubina, L.K.; Fedorov, S.N.; et al. Marine alkaloid monanchocidin A overcomes drug resistance by induction of autophagy and lysosomal membrane permeabilization. *Oncotarget* 2015, 6, 17328–17341. [CrossRef]

89. Tabakmakher, K.M.; Denisenko, V.A.; Dmitrenko, P.S.; Lee, Y.I.; Grishin, E.V.; Stonik, V.A. Monanchomycales A and B, new hybrid pentacyclic guanidine alkaloids from the Far-Eastern marine sponge *Monanchora pulchra*. *Tetrahedron Lett.* 2012, 53, 4228–4231. [CrossRef]

90. Korolkova, Y.; Makarieva, T.; Tabakmakher, K.; Shubina, L.; Kudryashova, E.; Andreev, Y.; Mosharova, I.; Lee, H.S.; Lee, Y.J.; Kozlov, S. Marine cyclic guanidine alkaloids monanchomycalin B and urupocidin A act as inhibitors of TRPV1, TRPV2 and TRPV3 but not TRPA1 receptors. *Mar. Drugs* 2017, 15, 87. [CrossRef] [PubMed]

91. Tabakmakher, K.M.; Denisenko, V.A.; Guzii, A.G.; Dmitrenko, P.S.; Dyshlovoy, S.A.; Lee, H.S.; Makarieva, T.N. Monanchomycales C, a new pentacyclic guanidine alkaloid from the Far-Eastern marine sponge *Monanchora pulchra*. *Nat. Prod. Commun.* 2013, 8, 1399–1402. [PubMed]

92. Tabakmakher, K.M.; Makarieva, T.N.; Denisenko, V.A.; Guzii, A.G.; Dmitrenko, P.S.; Kuzmich, A.S.; Stonik, V.A. Monanchoxymycales A and B, new hybrid pentacyclic guanidine alkaloids from the Far-Eastern marine sponge *Monanchora pulchra*. *Nat. Prod. Commun.* 2016, 11, 1817–1820.

93. Campos, P.E.; Queiroz, E.F.; Marcourt, L.; Wolfender, J.M.; Sanchez, A.S.; Illien, B.; Al-Mourabit, A. Guavin-Bialecki, A. Isolation and identification of new secondary metabolites from the marine sponge *Monanchora unguiculata*. *Planta Med.* 2016, 81, P580. [CrossRef]

94. Campos, P.E.; Wolfender, J.M.; Queiroz, E.F.; Marcourt, L.; Al-Mourabit, A.; Frederich, M.; Bordignon, A.; De Voogd, N.; Illien, B.; Guavin-Bialecki, A. Unguiculin A and ptilomycalins E–H, antimalarial guanidine alkaloids from the marine sponge *Monanchora unguiculata*. *J. Nat. Prod.* 2017, 80, 1404–1410. [CrossRef] [PubMed]

95. Guzii, A.G.; Makarieva, T.N.; Korolkova, Y.V.; Andreev, Y.A.; Mosharova, I.V.; Tabakmaher, K.M.; Denisenko, V.A.; Dmitrenok, P.S.; Ogurtsova, E.K.; Antonov, A.S.; et al. Pulchranin A, isolated from the Far-Eastern marine sponge, *Monanchora pulchra*. The first marine non-peptide inhibitor of TRPV-1 channels. *Tetrahedron Lett.* 2013, 54, 1247–1250. [CrossRef]

96. Makarieva, T.N.; Ogurtsova, E.K.; Korolkova, Y.V.; Andreev, Y.A.; Mosharova, I.V.; Tabakmaher, K.M.; Guzii, A.G.; Denisenko, V.A.; Dmitrenok, P.S.; Lee, H.S.; et al. Pulchranins B and C, new acyclic guanidine alkaloids from the Far-Eastern marine sponge *Monanchora pulchra*. *Nat. Prod. Commun.* 2013, 8, 1229–1232. [PubMed]

97. Ogurtsova, E.K.; Makarieva, T.N.; Korolkova, Y.V.; Andreev, Y.A.; Mosharova, I.V.; Denisenko, V.A.; Dmitrenok, P.S.; Lee, Y.I.; Grishin, E.V.; Stonik, V.A. New derivatives of natural acyclic guanidine alkaloids with TRPV2 receptor-regulating properties. *Nat. Prod. Commun.* 2015, 10, 1171–1173. [PubMed]

98. Dyshlovoy, S.A.; Tabakmakher, K.M.; Hauschild, J.; Shchekateva, R.K.; Otte, K.; Guzii, A.G.; Makarieva, T.N.; Kudryashova, E.K.; Fedorov, S.N.; Shubina, L.K.; et al. Guanidine alkaloids from the marine sponge *Monanchora pulchra* show cytotoxic properties and prevent EGF-Induced neoplastic transformation in vitro. *Mar. Drugs* 2016, 14, 133. [CrossRef] [PubMed]

99. El-Demerdash, A. Isolation of Bioactive Marine Natural Products and Bio-Inspired Synthesis of Fused Guanidinic Tricyclic Analogues. Unpublished Ph.D. Thesis, University of Paris-Saclay, Paris, France, May 2016.

100. El-Demerdash, A.; Moriou, C.; Martin, M.T.; Petek, S.; Debitus, C.; Al-Mourabit, A. Unguiculins A–C: Cytotoxic bis-guanidine alkaloids from the French Polynesian sponge, *Monanchora n. sp.* *Nat. Prod. Res.* 2017, 1–6. [CrossRef] [PubMed]

101. Kapustina, I.I.; Tabakmakher, K.M.; Makar’eva, T.N. Sterols from the toxin containing Far-Eastern sponge *Monanchora pulchra*. *Chem. Nat. Compd.* 2012, 47, 1025–1027. [CrossRef]
103. Wang, W.; Mun, B.; Lee, Y.; Reddy, M.V.; Park, Y.; Lee, J.; Kim, H.; Hahn, D.; Chin, J.; Ekins, M.; et al. Bioactive sesterterpenoids from a Korean sponge Monanchora sp. *J. Nat. Prod.* 2013, 76, 170–177. [CrossRef] [PubMed]

104. Mun, B.; Wang, W.; Kim, H.; Hahn, D.; Tang, I.; Won, D.H.; Kim, E.H.; Lee, J.; Han, C.; Kim, H.; et al. Cytotoxic 5a,8a-epidioxy sterols from the marine sponge Monanchora sp. *Arch. Pharm. Res.* 2015, 38, 18–25. [CrossRef] [PubMed]

105. Wang, W.; Lee, T.G.; Patil, R.S.; Mun, B.; Yang, I.; Kim, H.; Hahn, D.; Won, D.H.; Lee, J.; Lee, Y.; et al. Monanchosterols A and B, bioactive bicyclo[4.3.1] steroids from a Korean sponge Monanchora sp. *J. Nat. Prod.* 2015, 78, 368–373. [CrossRef] [PubMed]

106. Snider, B.B.; Shi, Z.J. Biomimetic synthesis of the bicyclic guanidine moieties of crambines A and B. *J. Org. Chem.* 1992, 57, 2526–2528. [CrossRef]

107. Snider, B.B.; Faith, W.C. The total synthesis of (±)-ptilocaulin. *Tetrahedron Lett.* 1983, 24, 861–864. [CrossRef]

108. Snider, B.B.; Faith, W.C. Total synthesis of (+)- and (−)-ptilocaulin. *J. Am. Chem. Soc.* 1984, 106, 1443–1445. [CrossRef]

109. Yu, M.; Pochapsky, S.; Snider, B.B. Synthesis of 7-Epineoptilocaulin, mirabilin B and isoptilocaulin. A unified biosynthetic proposal for the ptilocaulin and batzelladine alkaloids. Synthesis and structure revision of netamines E and G. *J. Org. Chem.* 2008, 73, 9065–9074. [CrossRef] [PubMed]

110. Black, G.P.; Murphy, P.J.; Walshe, N.D.A.; Hibbs, D.E.; Hursthouse, M.B.; Malik, K.M.A. A short synthetic route to the tricyclic guanidinium core of the batzelladine alkaloids. *Tetrahedron Lett.* 1996, 37, 6943–6946. [CrossRef]

111. Ahmed, N.; Brahmbhatt, K.G.; Singh, I.P.; Bhutani, K.K. Total synthesis of (±) batzelladine K: A biomimetic approach. *Synthesis* 2010, 15, 2567–2570. [CrossRef]

112. Snider, B.B.; Shi, Z. Biomimetic synthesis of the pentacyclic nucleus of ptelimycalin A. *J. Am. Chem. Soc.* 1994, 116, 549–557. [CrossRef]

113. Moore, C.G.; Murphy, P.J.; Williams, H.L.; McGown, A.T.; Smith, N.K. A synthesis of crambescidin 359. *Tetrahedron Lett.* 2003, 44, 251–254. [CrossRef]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).