Review

Marine Pharmacology in 2014–2015: Marine Compounds with Antibacterial, Antidiabetic, Antifungal, Anti-Inflammatory, Antiprotozoal, Antituberculosis, Antiviral, and Anthelmintic Activities; Affecting the Immune and Nervous Systems, and Other Miscellaneous Mechanisms of Action

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Abstract: The systematic review of the marine pharmacology literature from 2014 to 2015 was completed in a manner consistent with the 1998–2013 reviews of this series. Research in marine pharmacology during 2014–2015, which was reported by investigators in 43 countries, described novel findings on the preclinical pharmacology of 301 marine compounds. These observations included antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral, and anthelmintic pharmacological activities for 133 marine natural products, 85 marine compounds with antidiabetic, and anti-inflammatory activities, as well as those that affected the immune and nervous system, and 83 marine compounds that displayed miscellaneous mechanisms of action, and may probably contribute to novel pharmacological classes upon further research. Thus, in 2014–2015, the preclinical marine natural product pharmacology pipeline provided novel pharmacology as well as new lead compounds for the clinical marine pharmaceutical pipeline, and thus continued to contribute to ongoing global research for alternative therapeutic approaches to many disease categories.

Keywords: drug; marine; chemical; metabolite; natural product; pharmacology; pharmaceutical; review; toxicology; pipeline

1. Introduction

The aim of the present review is to consolidate 2014–2015 preclinical marine pharmacology, with a format similar to the previous nine reviews of this series, which cover the period 1998–2013 [1–9]. The peer-reviewed articles were retrieved from searches in the following databases: MarinLit, PubMed, Chemical Abstracts®, ISI Web of Knowledge, and Google Scholar. As in our previous work, we have limited our review to include bioactivity and/or pharmacology of structurally characterized marine
chemicals, which we have classified using a modification of Schmitz’s chemical classification [10] into six major chemical classes, namely, polyketides, terpenes, peptides, alkaloids, shikimates, and sugars. The preclinical antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral, and anthelmintic pharmacology of marine chemicals is reported in Table 1, with the structures shown in Figure 1. Marine compounds that affected the immune and nervous systems, with antidiabetic and anti-inflammatory effects, are exhibited in Table 2, with their respective structures consolidated in Figure 2. Finally, marine compounds affecting a variety of cellular and molecular targets are noted in Table 3, and their structures are shown in Figure 3.

Several publications during 2014–2015 reported on several marine extracts or structurally uncharacterized compounds, with novel preclinical and/or clinical pharmacology: in vitro phenotype-guided the discovery of natural products using cytological profiling to predict modes of action of bioactive constituents in extracts [11]; Colombian and Brazilian marine organisms as source of antibacterial extracts with bacterial quorum sensing inhibitory activity [12]; a first report describing antimicrobial activity in extracts from cultivable fungi associated with Antarctic marine sponges [13]; an extensive study on the antimicrobial activity of crude extracts from several species of red algae from Madagascar [14]; bioactive compounds along with a purified macrolactin with broad spectrum antibacterial activity in crude extracts from B. subtilis MTCC10403 associated with the Indian brown seaweed A. longifolius [15]; potential β-lactamase inhibitory activity in a Bay of Bengal marine Streptomyces sp. PM49 with antibacterial properties on multidrug-resistant pathogens [16]; in vitro anti-inflammatory activity of an extract and individual components in the spiny seastar M. glacialis that inhibited “different levels of the inflammation pathway” [17]; in vitro anti-inflammatory activity of several galactolipids isolated from methanol extracts of cultivated red alga Chondrus crispus that were proposed “to counter inflammation associated with NO-mediated disorders” [18]; in vitro immunomodulatory activity of an extract of the Bohai sea ascidian Styela clava that exhibited proliferative activity and promoted nitric oxide (NO) release from mouse lymphocytes and macrophages [19]; in vivo anti-inflammatory activity of a new nucleoside, dragmacidoside isolated from an extract of a marine Red sea sponge Dragmacidon coccinea [20]; in vivo anti-inflammatory and analgesic activities of an organic extract and its semipurified fractions from the Tunisian gorgonian Eunicella singularis, which suggested that “components of the active fraction can be used to treat various anti-inflammatory diseases” [21]; in vitro anti-inflammatory activity of 30 compounds in a methanol extract of the digestive gland of the Mediterranean sea hare Aplysia depilans, which could provide “beneficial anti-inflammatory effects” [22]; and, as part of anti-obesity nutraceuticals research, the anti-adipogenic activity of phlorotannins isolated from the edible brown alga Ecklonia cava were reported to be a “promising source for utilization against obesity and related complications” [23].

2. Marine Compounds with Antibacterial, Antifungal, Antiprotozoal, Antituberculosis, Antiviral, and Anthelmintic Activities

Table 1 presents 2014–2015 preclinical pharmacological research on the antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral, and anthelmintic activities of marine natural products (1–133) shown in Figure 1.
Table 1. Marine pharmacology in 2014–2015: marine compounds with antibacterial, antifungal, antituberculosis, antiprotozoal, antiviral, and anthelmintic activities.

| Drug Class       | Compound/Organism * | Chemistry | Pharmacologic Activity                                      | IC₅₀ b | MMOA b                      | Country c | References |
|------------------|---------------------|-----------|-------------------------------------------------------------|--------|----------------------------|-----------|------------|
| Antibacterial    | axinellamines A and B (1, 2)/sponge | Alkaloid f | Gram-positive and negative inhibition                        | 0.5–32 µg/mL  | Normal cellular division inhibition | USA [24] |            |
| Antibacterial    | buanmycin (3)/bacterium     | Polysaccharide d | S. enterica inhibition                                      | 0.7 µM  | Sorate A inhibition            | S. KOR [25] |            |
| Antibacterial    | cathelicidin (4)/sea snake | Peptide f  | Gram-positive and negative inhibition                        | 0.16–20.7 µg/mL | Membrane morphology alteration  | CHN [26] |            |
| Antibacterial    | clavanin A (5)/ascidian    | Peptide f  | S. aureus and E. coli infection                              | 10 mg/kg  | IL-6 and TNF-α inhibition    | BRA [27] |            |
| Antibacterial    | dieckin A (6)/sponge      | Terpenoid e | C. trachomatis inhibition                                    | 2.34 µM  | OmpA protein inhibition      | EGY, GBR [28] |            |
| Antibacterial    | ianthelliformisamamines B and C (7, 8)/sponge | Alkaloid f | Enhanced antibiotics against E. aerogenes, P. aeruginosa, K. Pneumoniae MDR strains in vitro | 3.12–12.5 µM  | Enhancement of drug transporters | FRA [29] |            |
| Antibacterial    | pardaxin (9)/flatfish    | Peptide f  | MR S. aureus inhibition in vivo                              | 8 mg/mL  | MCP-1, IL-6, and TNF-α inhibition | TWN [30] |            |
| Antibacterial    | phlorofucofuroeckol-A (10)/algae | Polysaccharide d | MR S. aureus inhibition                                      | 32 µg/mL  | PBP2a suppression             | S. KOR [31] |            |
| Antibacterial    | salinamide F (11)/bacterium | Polysaccharide d | E. coli inhibition                                      | 0.2 µg/mL  | RNA polymerase inhibition    | USA [32] |            |
| Antibacterial    | piscidins (12, 13)/fish   | Peptide f  | K. pneumonia and A. baumannii inhibition in vitro           | 1.5–3.1 µM | Undetermined                 | TWN [33] |            |
| Antibacterial    | admetazine A (14)/fungus  | Terpenoid e | S. aureus inhibition                                        | 8 µg/mL  | Undetermined                 | CHN [34] |            |
| Antibacterial    | agelamadins A and B (15, 16)/sponge Aspergillus sp. butyrolactone (17)/fungus | Alkaloid f | M. luteus and C. neoformans inhibition                      | 5–8 µg/mL  | Undetermined                 | AUS, JPN [35] |            |
| Antibacterial    | ausatile R (19)/fungus    | Terpenoid e | S. aureus and B. cereus inhibition                           | 1.56 µM  | Undetermined                 | CHN [36] |            |
| Antibacterial    | azonapylprone A (18)/fungus | Terpenoid e | S. aureus and B. subtilis inhibition                         | 8 µg/mL  | Undetermined                 | PRT, THAI [37] |            |
| Antibacterial    | citriplin B (20)/fungus   | Terpenoid e | Marine bacteria inhibition                                    | 0.1 µg/mL | Undetermined                 | CHN [38] |            |
| Antibacterial    | desmethylisaridin C1 (21)/fungus D. granoal dasphenyl ethers (22, 23)/sponge | Polysaccharide d | S. aureus inhibition                                      | 4 µg/mL  | Undetermined                 | CHN [39] |            |
| Antibacterial    | diaporthalasin (24)/fungus | Terpenoid e | E. coli inhibition                                          | 8 µg/mL  | Undetermined                 | CHN [40] |            |
| Antibacterial    | D. pulchra furanones (25, 26)/algae | Peptide f  | Gram-positive and negative inhibition                        | 1–16 µg/mL | Undetermined                 | USA [41] |            |
| Antibacterial    | aureol B (27)/sponge      | Terpenoid e | MR S. aureus inhibition                                      | 2 µg/mL  | Undetermined                 | THAI [42] |            |
| Antibacterial    | dysidin A (28)/sponge     | Terpenoid e | P. aeruginosa biofilm inhibition                             | 1.3 µM  | Undetermined                 | BRA, FRA, USA [43] |            |
| Antibacterial    | Eunicea sp. compounds (29, 30)/sponge | Terpenoid e | P. aeruginosa and S. aureus biofilm inhibition               | 0.5 mg/mL | Undetermined                 | COL [44] |            |
| Drug Class | Compound/Organism | Chemistry | Pharmacologic Activity | IC₅₀ b | MMOA b | Country c | References |
|-----------|------------------|-----------|------------------------|--------|--------|-----------|------------|
| Antibacterial | flavipesin A (31)/fungus | Polyketide d | S. aureus and B. subtilis inhibition | 0.25–8 µg/mL * | Undetermined | CHN [47] |
| Antibacterial | gageopeptides A–D (32–35)/bacterium | Peptide f | S. aureus and B. subtilis inhibition | 0.04–0.08 µM * | Undetermined | CHN [48] |
| Antibacterial | gageotetra A–C (36–38)/bacterium | Peptide f | S. aureus and B. subtilis inhibition | 0.02–0.04 µM * | Undetermined | CHN [49] |
| Antibacterial | hormaamycin B (39)/bacterium | Peptide f | S. aureus and K. rhizophila inhibition | 0.4–7 µM * | Undetermined | S. KOR [50] |
| Antibacterial | iedoglucomide C (40)/bacterium | Glycolipid | Gram-positive and negative inhibition | 0.01–0.05 µM * | Undetermined | S. KOR [51] |
| Antibacterial | isoikarugamycin (41)/bacterium | Alkaloid f | MR S. aureus | 2–4 µg/mL * | Undetermined | ESP [52] |
| Antibacterial | keramadine (42)/sponge | Terpenoid e | M. luteus inhibition | 4 µg/mL * | Undetermined | AUS, JPN [53] |
| Antibacterial | Ircinia sp. secosterols (43, 44)/sponge | Terpenoid e | M. luteus and S. epidermidis inhibition | 3.1, 6.3 µg/mL | Undetermined | S. KOR [54,55] |
| Antibacterial | L. dendyi terpenoids (45, 46)/sponge | Polyketide d | MR S. aureus inhibition | 0.05–0.29 µM | Undetermined | USA [56] |
| Antibacterial | lindgomycin (47)/fungus | Polyketide d | MR S. aureus inhibition | 5.1 µg/mL | Undetermined | CHN, DEU [57] |
| Antibacterial | marformysin D (48)/bacterium | Peptide f | M. luteus inhibition | 0.063 µg/mL * | Undetermined | CHN [58] |
| Antibacterial | mollenycin A (49)/bacterium | Terpenoid e | S. typhi and S. aureus inhibition | 7.5 µg/mL | Undetermined | MYS [60] |
| Antibacterial | neolaurene (50)/alga | Alkaloid f | S. aureus inhibition | 0.3 µg/mL * | Undetermined | CHN [61] |
| Antibacterial | penicyclone A (51)/fungus | Polyketide d | S. aureus inhibition | 2 µg/mL * | Undetermined | CHN [62] |
| Antibacterial | P. oxalicum enamide (52)/fungus | Terpenoid e | B. cereus and S. aureus inhibition | 10 µg/disk * | Undetermined | USA, USA [63] |
| Antibacterial | pupehenol (53)/sponge | Terpenoid e | B. cereus and S. aureus inhibition | 2.5–3.3 µg/mL * | Undetermined | EGY, GBR [64] |
| Antibacterial | phyllospongion E (54)/sponge | Terpenoid e | MR S. aureus inhibition | 1.5–4.3 µM * | Undetermined | SAU [65] |
| Antibacterial | sartocrochiol (55, 56)/soft coral | Terpenoid e | MR S. aureus inhibition | 2 µM | Undetermined | CHN, DEU [66] |
| Antibacterial | spiromastixone J (57)/fungus | Polyketide d | MR S. aureus inhibition | 1.4–1.7 µM | Undetermined | CHN, DEU [67] |
| Antibacterial | stachyin B (58)/fungus | Terpenoid e | MR S. aureus and B. subtilis inhibition | 1.4–1.7 µM | Undetermined | CHN, DEU [67] |
| Antibacterial | Streptomyces sp. glycoside (59)/bacterium | Polyketide d | C. trachomatis inhibition | 4.03 µM | Undetermined | EGY, DEU [68] |
| Antibacterial | subergosterones A–C (60–62)/gorgonian coral | Terpenoid e | B. cereus inhibition | 1.6–3.1 µM * | Undetermined | CHN [69] |
| Antibacterial | vitroproacine A (63)/bacterium | Polyketide d | A. baumannii inhibition | 8 µg/mL * | Undetermined | TWN, USA [70] |
| Antibacterial | xestospongiamide (64)/sponge | Polyketide d | Gram-positive and negative inhibition | 2.5 µM * | Undetermined | EGY, SAU [71] |
| Antifungal | bahamaolide A (65)/bacterium | Polyketide d | C. albicans inhibition | 1.5–3.1 µg/mL * | ICL inhibition | S. KOR [72] |
| Antifungal | heronamide C (66)/bacterium | Polyketal/alkaloid f | S. pombe cell inhibition | 5.8 µM * | Alteration of membrane microdomains | JPN [73] |
| Antifungal | forazoline A (67)/bacterium | Polyketide d | C. albicans inhibition | 16 µg/mL * | Affected membrane integrity | USA [74] |
| Antifungal | aaptamine derivative (68)/sponge | Alkaloid f | T. rubrum inhibition | 4 µg/mL * | Undetermined | CHN [75] |
Table 1. Cont.

| Drug Class     | Compound/Organism *                  | Chemistry        | Pharmacologic Activity             | IC<sub>50</sub> b | MMOA b  | Country c | References |
|----------------|-------------------------------------|------------------|-----------------------------------|-------------------|---------|-----------|------------|
| Antifungal     | amphidinin G (69)/dinoflagellate    | Polyketide d     | T. mentagrophytes inhibition       | 8 µg/mL           | Undetermined | JPN [76]  |
| Antifungal     | amphidinol 18 (70)/dinoflagellate   | Polyketide d     | C. albicans inhibition            | 9 µg/mL           | Undetermined | ITA [77]  |
| Antifungal     | crambescin homologues (71–73)/sponge| Alkaloid f       | C. neoformans var. gattii inhibition | 0.85-2.6 µM *     | Undetermined | USA [78]  |
| Antifungal     | coustesides C and D (74, 75)/sea   | Terpenoid glycoside e | C. albicans inhibition           | 1 mg/mL **        | Undetermined | EGY, S.KOR [79] |
| Antifungal     | L. okamurai laurenes (76–78)/alga  | Terpenoid e      | C. albicans inhibition            | 2–4 µg/mL **      | Undetermined | CHN, S. KOR [80,81] |
| Antifungal     | pleosporallin E (80)/fungus        | Polyketide d     | C. albicans inhibition            | 4.4 µM            | Undetermined | CHN [82]  |
| Antifungal     | S. purpurea lysophospholipid (81)/sponge| Phospholipid   | C. albicans and C. neoformans inhibition | 7.44 µg/mL +     | Undetermined | CHN [84]  |
| Antifungal     | taurospongin A (82)/sponge         | Polyketide d     | C. neoformans inhibition           | 1 µg/mL +         | Undetermined | AUS, JPN [85] |
| Antifungal     | variegatuside D (83)/sea camburer  | Terpenoid glycoside e | Several Candida species inhibition | 3.4–13.6 µg/mL + | Undetermined | CHN [86]  |
| Antifungal     | xestospongiamide (64)/sponge       | Polyketide d     | A. niger and C. albicans inhibition | >5 µM *           | Undetermined | EGY, SAU [71] |
| Antimalarial   | C. hooperi isonitrile (84)/sponge  | Terpenoid e      | P. falciparum D6 and W2 strain inhibition | 4.3–4.7 nM       | β-hematin inhibition | USA, ZAF [87] |
| Antimalarial   | actinoramide A (85)/bacterium      | Peptide f        | P. falciparum strains inhibition | 0.2 µM           | Undetermined | CRI, USA [88] |
| Antimalarial   | diacarperoxide J (86)/sponge       | Terpenoid e      | P. falciparum D6 and W2 strain inhibition | 1.6–1.8 µM      | Undetermined | CHN, USA [89] |
| Antimalarial   | laevigatol A (87)/soft coral       | Terpenoid e      | P. falciparum NF54 strain inhibition | 3.0 µM          | Undetermined | CHE, DEU, S. KOR, VNM [90] |
| Antimalarial   | mollemycin A (49)/bacterium        | Polyketide d     | P. falciparum 3D7 and Dd2 strain inhibition | 7–9 nM          | Undetermined | AUS [59]  |
| Antimalarial   | mon amphielines B and C (88, 89)/sponge| Terpenoid e      | P. falciparum 3D7 strain inhibition | 44 nM           | Undetermined | USA [91]  |
| Antimalarial   | netamine K (90)/sponge             | Alkaloid f       | P. falciparum inhibition           | 2.4 µM           | Undetermined | BEL, FRA, ISR [92] |
| Antimalarial   | P. ocella sesquiterpenes (91–93)/nudibranch | Terpenoid e | P. falciparum inhibition | 0.26–0.3 µM | Undetermined | AUS, ITA [93] |
| Antimalarial   | P. simplex polyketide (94)/sponge  | Polyketide d     | P. falciparum D10 and W2 strain inhibition | 2.7–4.0 µM     | Undetermined | CHN, ITA [94] |
| Antiprotozoal  | plakortide E (95)/sponge            | Polyketide d     | T. brucei inhibition              | 5 µM             | Rhodesin inhibition | EGY, DEU [95] |
| Antiprotozoal  | batzelladine L (96)/sponge          | Alkaloid f       | T. cruzi and L. infantum inhibition | 2 µM            | Enhanced ROS generation | BRA, CAN [96] |
| Drug Class          | Compound/Organism *   | Chemistry | Pharmacologic Activity | IC₅₀ b   | MMOA b | Country c | References |
|---------------------|-----------------------|-----------|------------------------|----------|-------|-----------|------------|
| Antiprotozoal       | actinoporin A (97) / bacterium | Polyketide d | T. b. brucei inhibition | 15 µM    | Undetermined | AUS, DEU, EGY, GBR, DEU, VNM, S. KOR, IRL, GBR | [97] |
| Antiprotozoal       | astrepectenol A (98) / soft coral | Terpenoid e | T. brucei inhibition | 1.6 µM   | Undetermined | | [98] |
| Antiprotozoal       | H. simulans sterol (99) sponge | Terpenoid e | T. b. brucei inhibition | 4.6 µM * | Undetermined | USA | [99] |
| Antiprotozoal       | lobosamide A (100) / bacterium | Alkaloid f | T. b. brucei inhibition | 0.8 µM   | Undetermined | | [100] |
| Antiprotozoal       | lobocrasols A and C (101, 102) / soft corals | Terpenoid e | L. donovani inhibition | 0.18 µM  | Undetermined | | [90] |
| Antiprotozoal       | mangromicin A (103) / fungus | Polyketide d | T. b. brucei inhibition | 2.44 µg/mL | Undetermined | USA | [101] |
| Antiprotozoal       | crassumols D and E (104, 105) / soft corals | Terpenoid e | T. b. rhodesiense inhibition | 0.61 and 0.72 µM | Undetermined | | [90] |
| Antiprotozoal       | sesterstamide (106) / sponge | Terpenoid e | L. donovani inhibition | 32.9 µg/mL | Undetermined | CHN | [102] |
| Antiprotozoal       | shagene A (107) / soft coral | Alkaloid f | M. smegmatis inhibition | 5 µM | Undetermined | AUS, USA | [103] |
| Antituberculosis    | aaptamine analog (108) / sponge | Peptide f | M. tuberculosis inhibition | 6.25 µg/mL * | Undetermined | JPN | [104] |
| Antituberculosis    | callyaerins A and B (109, 110) / sponge | Alkaloid f | M. tuberculosis H₃Rv inhibition | 2.5 µM ** | Undetermined | CHN, DEU, NLD | [105] |
| Antituberculosis    | denigrin C (111) / sponge | Alkaloid f | M. tuberculosis H₃Rv inhibition | 4 µg/mL * | Undetermined | IND | [106] |
| Antituberculosis    | oxazinin A (112) / fungus | Alkaloid f | M. tuberculosis H₃Rv inhibition | 2.9 µM | Undetermined | USA | [107] |
| Antiviral            | pateamine A (113) / sponge | Mixed Biogenesis | Sindbis virus mRNA translation inhibition | >100 nM | | CAN, ESP, NZL | [108] |
| Antiviral            | abyssomicin 2 (114) / bacterium | Polyketide d | HIV-1 reactivation | 13.9 µM | | Increased viral RNA in CD4+ T cells Reverse transcriptase inhibition Virion assembly/release inhibition | USA | [109] |
| Antiviral            | 8,4'-dieckol (115) / alga | Polyketide d | HIV-1 inhibition | 10 µM * | | | S. KOR | [110] |
| Antiviral            | truncateol M (116) / fungus | Terpenoid e | H1N1 influenza A virus inhibition | 8.8 µM | | CHN, DEU | [111] |
| Antiviral            | neoechinulin B (117) / fungus | Alkaloid f | H3N2, H1N1 A influenza virus inhibition | 17-22 µM | | CHN, DEU | [112] |
| Antiviral            | thaixylomolin I (118) / mangrove | Terpenoid e | H1N1 influenza A virus inhibition | 77 µM | | CHN, DEU, THAI | [113] |
Table 1. Cont.

| Drug Class | Compound/Organism * | Chemistry | Pharmacologic Activity | IC₅₀ b | MMOA b | Country c | References |
|------------|---------------------|-----------|------------------------|--------|--------|-----------|------------|
| Antiviral  | aaptamine derivative (68)/sponge | Alkaloid f | HIV-1 inhibition | 10 µM * | Undetermined | CHN | [75] |
| Antiviral  | aflaquinolone B derivative (119)/fungus | Mixed biogenesis | HSV inhibition | 0.042 µM | Undetermined | CHN | [114] |
| Antiviral  | A. terreus lactones (120, 121)/fungus | Polyketide d | HSV-1 inhibition | 6.34 µg/mL | Undetermined | CHN | [115] |
| Antiviral  | chartarutine B (122)/fungus | Alkaloid f/terpenoid e | HIV-1 inhibition | 4.9 µM | Undetermined | CHN, DEU | [116] |
| Antiviral  | debromoaplysiatoxin (123)/cyanobacterium | Polyketide d | CHIKV inhibition | 1.4 µM | Undetermined | NZL, SGP | [117] |
| Antiviral  | dolabellaclenol A (124)/alga | Terpenoid e | HIV-1 inhibition | 2.9 µM | Undetermined | BRA, COL, ESP | [118] |
| Antiviral  | D. plectens diterpene (125)/alga | Terpenoid e | HIV-1 inhibition | 16.1 µM | Undetermined | CHN | [119] |
| Antiviral  | Dysidea sp. PBDEs (22, 23)/sponge | Polyketide d | Hepatitis B inhibition | 0.23–0.80 µM | Core promoter inhibition | IDN, JPN, NLD | [120] |
| Antiviral  | echrebsteroid C (126)/gorgonian | Terpenoid e | RSV inhibition | 0.19 µM | Undetermined | CHN | [121] |
| Antiviral  | (+)-pestaloxazine A (127)/fungus | Alkaloid f | Enterovirus 71 inhibition | 14.2 µM | Undetermined | CHN | [122] |
| Antiviral  | phlorofucofuroeckol-A (10)/alga | Polyketide d | MNV inhibition | 0.9 µM | Undetermined | S. KOR | [123] |
| Antiviral  | sporeolide B (129)/bacterium | Terpenoid e | HCMV inhibition | 5 µg/mL | Undetermined | TWN | [124] |
| Antiviral  | stellettapeptins A and B (130, 131)/sponge | Polyketide d | HIV-reverse transcriptase inhibition | 14 µM | Undetermined | IND | [125] |
| Antiviral  | trichoboteris A (132)/fungus | Peptide f | HIV-1 infection inhibition | 23–27 nM | Undetermined | USA | [126] |
| Anthelmintic | phorioadenine A (133)/sponge | Alkaloid f | H. contortus inhibition | 31 µg/mL +++ | Undetermined | AUS | [128] |

* Organism: Kingdom Animalia: ascidian, Batfish, sea snakes (Phylum Chordata), gorgonian, coral (Phylum Cnidaria), sea cucumber (Phylum Echinodermata), nudibranch (Phylum Mollusca), sponge (Phylum Porifera); Kingdom Monera: bacterium (Phylum Cyanobacteria); Kingdom Fungi: fungus; Kingdom Plantae: alga, mangrove, seagrass; Kingdom Protista: dinoflagellates; b IC₅₀: concentration of a compound required for 50% inhibition in vitro, *: estimated IC₅₀, **: MIC₉₀, ***: in vivo study; + MIC: minimum inhibitory concentration, ++ MID: minimum inhibitory concentration per disk; *** L₉₀: concentration of a compound required for 90% lethality; b MMOA: molecular mechanism of action; c Country: AUS: Australia; BEL: Belgium; BGD: Bangladesh; BRA: Brazil; CAN: Canada; CHE: Switzerland; CHN: China; COL: Colombia; CRI: Costa Rica; DEL: Germany; EGY: Egypt; ESP: Spain; FRA: France; GBR: United Kingdom; IDN: Indonesia; IND: India; IRL: Ireland; ISR: Israel; ITA: Italy; JPN: Japan; MYS: Malaysia; NLD: The Netherlands; NZL: New Zealand; PRT: Portugal; SAU: Saudi Arabia; SGP: Singapore; S. KOR: South Korea; THAI: Thailand; TWN: Taiwan; VNM: Vietnam; ZAF: S. Africa; Chemistry: d polyketide; e terpene; f nitrogen-containing compound; g polysaccharide; h shikimate; Abbreviations: CHIKV: chikungunya virus; HCMV: human cytomegalovirus; MNV: murine norovirus; HSV: herpes simplex virus; ICL: isocitrate lyase; MR: methicillin-resistant; PBP2a: penicillin-binding protein 2a; RNAP: RNA-polymerase; RSV: respiratory syncytial virus; TNF-α: tumor necrosis factor α.
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Figure 1. Marine pharmacology in 2014–2015: marine compounds with antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral, and anthelmintic activities.

2.1. Antibacterial Activity

During 2014–2015, 48 studies reported antibacterial marine natural products (1–64) isolated from bacteria, fungi, tunicates, sponges, soft corals, sea snakes, fish, and algae; a research enterprise focused on the discovery of novel chemical leads to treat emerging drug-resistant bacterial infections.

As shown in Table 1 and Figure 1, nine publications reported on the mode of action of marine-derived antibacterial compounds. Rodríguez and colleagues reported on “a practical synthesis of the axinellamines” (1, 2), as well as their broad spectrum Gram-positive and Gram-negative antibacterial activity, probably resulting from “secondary membrane destabilization…consistent with the inhibition of normal septum formation” [24]. Moon and colleagues characterized a new pentacyclic antibiotic, buanmycin (3), isolated from a Korean marine *Streptomyces* strain, which was active towards Gram-native *Salmonella enterica* that causes salmonellosis, by inhibiting sortase A, an enzyme involved
in bacterial adhesion and proposed as a “promising target for antibiotic discovery” [25]. Wei and colleagues discovered a novel peptide cathelicidin (4) from the Chinese sea snake *Hydrophis cyanocinctus* with potent antimicrobial activity against 35 strains of 48 human pathogenic bacteria, probably by a mechanism that involved “disruption of cell membrane and lysis of bacterial cells . . . resulting in cellular disruption of both Gram-positive and Gram-negative bacteria” [26]. Silva and colleagues demonstrated that the antimicrobial peptide clavanin A (5) significantly reduced *E. coli* and *S. aureus*-infected mice mortality with concomitant reduction of proinflammatory cytokines, thus proposing that clavanin A “. . . will facilitate studies on the development of novel peptide-based strategies for the treatment of infected wounds and sepsis” [27]. Abdelmohsen and colleagues investigated the new sterol gelliusterol E (6) from the Red sea sponge *Callyspongia aff. impexa* and showed that it inhibited both the primary infection by *Chlamydia trachomatis*, an obligate intracellular Gram-negative bacterium, as well as the production of viable progeny, and thus the developmental cycle of this bacterium [28]. Pieri and colleagues described new ianthelliformisamine B and C (7, 8) from the marine sponge *Suberia ianthelliformis* as antibiotic enhancers against resistant Gram-negative bacteria by a mechanism described as “altered proton homeostasis”, and thus probably affecting drug transport [29]. Huang and colleagues showed that the antimicrobial peptide pardaxin (9) isolated from the Red sea flatfish *Pardachirus marmoratus* protected mice from a lethal dose of methicillin-resistant *Staphylococcus aureus*, while also accelerating wound healing, increasing monocytes’ and macrophages’ recruitment, as well as expression of vascular endothelial growth factor [30]. Eom and colleagues described the mechanism of antibacterial activity of the phlorotannin phlorofucofuroeckol-A (10) isolated from the edible brown alga *Eisenia bicyclis*, which was shown to involve suppression of several *mec* operon genes in methicillin-resistant *Staphylococcus aureus* as well as the production of penicillin-binding protein 2a, considered as the “primary cause of methicillin resistance” [31]. Hassan and colleagues reported a new depsipeptide salinamide F (11), isolated from a marine-derived *Streptomyces* sp. strain CNB-091 that was observed to significantly inhibit RNA polymerase (RNAP) from both Gram-negative and Gram-negative bacteria, but “does not interact with the rifampin binding site on RNAP” [32].

As shown in Table 1 and Figure 1, 53 marine natural products (12–64), some of them novel, were reported to exhibit antibacterial activity with MICs <10 µg/mL or 10 µM against several Gram-positive and Gram-negative bacterial strains, although the mechanism of action for these compounds remained undetermined: two antimicrobial peptides, piscidins 3 and 4 (12, 13) originally isolated from the fish tilapia *Oreochromis niloticus* [33]; a new bisthiodiketopiperazine adametizine A (14), isolated from a marine sponge-derived fungus *Penicillium admetzioides* AS-53 [34]; two dimeric bromopyrrole alkaloids agelamadins A and B (15, 16), isolated from the Okinawan marine sponge *Agelas* sp. [35]; a butyrolactone derivative (17), isolated from the fermentation broth of a South China sea gorgonian *Muricella abnormalis*-derived *Aspergillus* sp. XS-20090B15 fungus [36]; a meroditerpene azsonapryrone A (18), isolated from the Thai marine sponge *Chondrilla asustraliensis*-associated fungus *Neosartorya paulistensis* (KUFC 7897) [37]; a new meroterpenoid, austalide R (19), from a fungus *Aspergillus* sp. isolated from the Mediterranean sponge *Tethya aurantium* [38]; a novel citrilfelin B (20) with a unique tetracyclic framework was characterized from a co-culture of marine-derived fungi *Penicillium citrinum* and *Beauveria felina* [39]; a novel cyclohexadepsipeptide desmethylsaradin C1 (21) identified from a marine bryozoan-derived fungus *Beauveria felina* EN-135 [40]; two novel polybrominated diphenyl ethers (22, 23), isolated from the cosmopolitan marine sponge *Dysidea* spp. [41]; a new pentacyclic cytochalasin diaporthalasin (24), isolated from the marine-derived fungus *Diaporthaceae* sp. PSU-SP2/4 [42]; natural brominated furanones (25, 26), isolated from the marine alga *Delisea pulchra* [43]; a novel meroterpenoid aureol B (27), isolated from the Micronesian *Dysidea* sp. sponge [44]; a novel meroterpenoid dysidinoid A (28), isolated from the South China sea sponge *Dysidea* sp. [45]; a terpenoid fuscoside E peracetate (29) and a lipid butyl alcohol (30), isolated from the Colombian soft coral *Eunicea* sp. [46]; a new aromatic butyrolactone flavipesin A (31), isolated from a marine-derived endophytic fungus *Aspergillus flavipes* [47]; new non-cytotoxic lipopeptides gageopeptides A–D (32, 33, 34, 35) [48] and gageotetritins A–C (36, 37, 38) [49], isolated from a Korean marine-derived *Bacillus subtilis* strain 109GGC020;
a new cyclic depsipeptide hormaomycin B (39), isolated from a Korean marine mudflat-derived actinomycete Streptomyces sp. strain SNM55 [50]; a new glycolipid iodeoglucosamide C (40) from the Korean marine-derived bacterium Bacillus licheniformis strain 09JIDYM23 [51]; a new polycyclic tetramic acid macro lactam isoikarugamycin (41) from Equatorial Guinean Streptomyces zhaozhounensis strain CA-185989 [52]; a bromopyrroloalkaloid keramidine (42), isolated from the Okinawan marine sponge Agelas sp. [53]; “unprecedented” 9,11 seco steroids with “the 2-ene-1,4-dione moiety” (43, 44) from the Korean marine sponge Irinicia sp. [54, 55]; two polybrominated diphenyl ethers (45, 46) from the Papuan New Guinea marine sponge Lendenfeldia dendyi and the soft coral Sinularia duru [56]; a novel polyketide lindgomycin (47) from the Baltic sea and Arctic Lindgomycetaceae family marine fungal strains KP970 and LF327 [57]; a novel cycloheptadepsipeptide marfomycin D (48), isolated from a South China sea Streptomyces drozdowiczi SCSIO 10141 [58]; an glycohexadepsipeptide-polyketide mollemonycin A (49) from an Australian marine-derived Streptomyces sp. strain CMB-M0244 [59]; a novel laurene-type sesquiterpene neolaurene (50) from a Bornean marine alga Laurencia nangii [60]; a new polyketide and ambucic analogue penicyclone A (51), isolated from an extract from a deep-sea derived fungus Penicillium sp. F23-2 [61]; a new phenolic enamide (52), characterized from the Chinese marine alga Codium fragile-derived endophytic fungus Penicillium oxalicum strain EN-290 [62]; a novel meroterpenoid pupehenol (53), isolated from a Hawaiian sponge Dactylospogia sp. [63]; a new scalarane sesterpenes phyllospongion E (54), isolated from the Egyptian Red sea sponge Phyllospongia lamellosa [64]; two new rare pyrene-based cebranoids ractochelols acetate (55) and sarcotrichelols (56), isolated from the Red sea soft coral Sarcophyton trochiophiliaorum [65]; a novel depsidone-based analogue spiromastixone J (57), isolated from the fermentation broth of a deep-sea Spiromasti x sp. fungus [66]; a new spirocyclic drimane stachyin B (58), identified in the mycelia and culture broth of a North sea Stachybotrys sp. fungus strain MF347 [67]; a naphthacene glycoside SF2446A2 (59), isolated from a culture of Streptomyces sp. strain RV15 derived from the Mediterranean sponge Dysidea tupha [68]; three new subergosterones A–C (60–62), obtained from the South China sea gorgonian coral Subergorgia rubra [69]; an amino-polyketide vitroprocin A (63), isolated from the marine bacterium Vibrio sp. strain QWI-06 [70]; and a new polyacetylene derivative xestospongiamide (64), isolated from the Red sea sponge Xestospongia sp. [71].

Furthermore, during 2014–2015, several other marine natural products, some of them novel, reported antimicrobial activity in MICs or IC₅₀’s ranging from 10 to 50 µg/mL, or 10–50 µM, respectively, and thus, because of their lower antibacterial potency, were excluded from Table 1 and Figure 1: tetracyclic sesterterpenes from a Korean marine sponge Clathria gombawuiensis sp. (MIC = 6.25–25 µg/mL) [129]; the antimicrobial peptide isolated from the mucus of the hagfish Myxine glutinosa and several structural analogs (MICs = 1.2–50 µM) [130]; bromopyrroloalkaloids agelamadins C–E (IC₅₀ = 32 µg/mL) from the Okinawan marine sponge Agelas sp. [131]; a new indole dit erpenoid from the fungus Aspergillus flavus (MIC = 20.5 µM), isolated from the Chinese prawn Penaeus vannamei [132]; two new bromopyrroloalkaloids isolated from the Okinawan sponge Agelas sp., namely 2-debromomonomogelamide U and 2-debromonomukadin G (MIC=32 µg/mL) [133]; seven known and one new sesquiterpene named epoxysuberbergoric acid isolated from the Chinese gorgonian coral S. suberosa (MIC=8 µg/mL) [134]; a new bromotyrosine alkaldol aplysamine 8 (MIC=31 µg/mL) from an Australian marine sponge Pseudocerotina purpurea [135], alternariol derivatives (MIC = 50 µg/disk) from the endophytic fungus Alternaria alternata isolated from the Red sea soft coral Litophyton arboretum [136]; new polyketides amphibins C–F (MIC = 16 and 32 µg/mL), isolated from the culture broth of dinoflagellate Amphidinium sp. [137]; a new 1-deoxysphingoid, 3-epi-xestoaminol C (MIC = 32.6 µM), isolated from the New Zealand brown alga Xiphophora chondrophylla [138]; a new cyclic pentapeptide, asperpeptide A (MIC = 12.5 µM), isolated from the gorgonian-derived fungus Aspergillus sp. [139]; a nucleoside derivative, kipukasin H (MIC = 12.5 µM), isolated from the fungus A. versicolor derived from the Xisha islands, South China sea gorgonian D. gemmacea [140]; a new O-containing heterocyclic compound named felinone B (MIC = 32 µg/mL) from an extract of B. feline EN-135, a fungus isolated from an unidentified marine bryozoan [141]; new xanthone microluside A (MIC = 10–13 µM) from a Red sea marine
sponge *S. vagabunda*-derived *Micrococcus* sp. EG45 [142]; a new cyclohexapeptide desotamide B (MIC = 12–16 µg/mL) from a South China sea marine microbe *S. scopuliridis* SCSIO ZJ46 [143]; new linear lipopeptides (MIC = 16 and 32 µg/mL) from a Korean marine *Bacillus subtilis* [144]; a new streptophenazine K (MIC = 14.5–21.6 µM) from bacteria isolated from a Baltic sea sponge *Halichondria panacea* [145]; a novel polyketide amantelide A (MIC = 32 µM) from a Guamanian Oscillatoriales cyanobacterium [146]; a novel echinomycin analog, quinomycin G (MIC = 16–64 µg/mL), isolated from *Streptomyces* sp. LS298 from a Hainan marine sponge *Gellides carcosa* [147]; and new cyclic lipopeptides gageopeptins A and B (MIC = 6 and 32 µg/mL) from a marine-derived strain *Bacillus* sp. 109GGC020 [144].

## 2.2. Antifungal Activity

Sixteen studies during 2014–2015 reported on the antifungal activity of several marine natural products (64–83) isolated from marine bacteria, dinoflagellates, sponges, sea cucumbers, and algae, a slight increase from our last review [9] and previous reviews of this marine pharmacology series.

As shown in Table 1 and Figure 1, three reports described antifungal marine chemicals with novel mechanisms of action. Lee and colleagues investigated the new macrocyclic lactone antifungal bahamaolide A (65) isolated from the culture of marine actinomycete *Streptomyces* sp. CNQ343 [72]. Detailed studies determined that the compound inhibited isocitrate lyase (ICL) mRNA expression, suggesting it might be used for treatment of “*C. albicans* infections via inhibition of ICL activity”. Sugiyama and colleagues characterized the biological activity of the polyene macrolactam heronamide C (66) isolated from a marine-derived *Streptomyces* sp. [73]. The heronamide C was shown to induce abnormal cell wall morphology by “perturbing membrane microdomains”. Wyche and colleagues reported a novel marine-derived polyketide forazoline A (67) isolated from an *Actinomadura* sp. strain WMMB-499 cultivated from the ascidian *Ecteinascidia turbinata* [74]. Using chemical genomics, the authors proposed forazoline A worked in vivo in mice against the fungus *Candida albicans* by affecting cell membrane integrity by a “novel mechanism of action from known antifungal agents”.

As shown in Table 1 and Figure 1, several marine natural products showed antifungal activity with MICs that were either less than 10 µg/mL, 10 µM, or 10 µg/disk, but no mechanism of action studies were reported in the papers: an alkaloid aaptamine derivative (68), isolated from the South China sea sponge *Aaptos aaptos* [75]; a new linear polyketide amphidinolin G (69), isolated from a Japanese symbiotic marine dinoflagellate *Amphidinium* sp. discovered in a marine flatworm *Amphiscolites* sp. [76]; a new polyketide amphidinol 18 (70), isolated from the dinoflagellate *Amphidinium carterae* strain CCMP121 [77]; new crambescin A2 (71–73), alkaloid homologues from the Bahamian marine sponge *Pseudaxinella reticulata* [78]; two new saponins couteaside C (74) and D (75), reported from the Egyptian Red sea cucumber *Bohadschia cousteaui* [79]; two new laurane-type sesquiterpenes, laurepoxyene (76) and 3β-hydroxyperoxyaplysin (77), and a new polyunsaturated fatty acid ethyl ester (78), isolated from the Chinese red alga *Laurencia okamurai* [80,81]; a novel dilactone-tethered pseudo-dimeric peptide mohangamide A (79), isolated from a Korean marine *Streptomyces* sp. [82]; a novel pleosporallin E (80), isolated from a marine fungus *Pleosporales* sp., discovered on the South China sea alga *Enteromorpha clathrata* [83]; a lysosphospholipid (81), isolated from the South China sea sponge *Spirastrella purpurea* [84]; an acetylenic fatty acid derivative taurospoming A (82) from an Okinawan marine sponge SS-1202, family *Spongidae* [85], and a new non-sulphated triterpene glycoside variegatuside D (83) from the south China sea cucumber *Stichopus variegates* [86]. Mechanism of action studies will be required to characterize the antifungal pharmacology of these marine-derived natural compounds.

In addition, novel structurally-characterized marine molecules with antifungal MICs or IC50’s greater than 10 µg/mL, 10 µM, or 10 µg/disk, which have been excluded from Table 1 and Figure 1 because of their weaker bioactivity: a new bromopyrrrole alkaloid mukanadine G (IC50 = 8–16 µg/mL) isolated from the Okinawan marine sponge *Agelas* sp. [53]; a new C24-acetylenic acid, biemnic acid (MIC = 100 µg/disk) isolated from the Red sea sponge *Biemna ehrenbergii* [148]; two sulfated steroid-aminoacid conjugates isolated from the Irish marine sponge *Polymastia boletiformis*...
(MIC = 100 µg/disk) against C. albicans [149]; two novel lysophospholipids from the Guanxi sponge S. purpurea (IC₅₀ = 16 and 32 µg/mL) [84]; two new bromotyrosine alkaloids, tyrokeridine G and H, isolated from an Okinawan Verongid marine sponge (MIC = 16 and 32 µg/mL) [150]; two highly brominated polyphenols isolated from the Qingdao red alga S. latiuscula (MIC = 12.5, 25 µg/mL) [151]; one novel anhydride metabolite, tubingenic anhydride A (MIC = 330 µM), from the Mediterranean fungus A. tubingenis (Strain OY907) [152]; and a novel compound terretrione D (MIC = 32 µg/mL) from a tunicate-derived fungus Penicillium sp. CYE-97 [153]. These novel marine compounds may contribute to the antifungal preclinical and clinical pipeline upon further research.

2.3. Antiprotozoal and Antituberculosis Activity

As shown in Table 1, during 2014–2015, twenty-four studies contributed to novel findings on antiprotozoal (antimalarial, antileishmanial, and antitrypanosomal) and antituberculosis pharmacology of structurally characterized marine natural products (84–112), very similar to our previous 1998–2013 marine pharmacology reviews [1–9].

Malaria, a global disease caused by protozoan genus Plasmodium (P. falciparum, P. ovale, P. vivax and P. malariae), currently affects over 2 billion people worldwide. Contributing to the global search for novel antimalarial drugs, and as presented in Table 1, 11 marine molecules (84–94) isolated from bacteria, molluscs, sponges, and soft corals were shown during 2014–2015 to possess antimalarial activity. Young and colleagues reported a detailed mechanistic study with the marine sesquiterpene isonitrile (MIC Leishmania (L. potente a antimalarial activity against drug sensitive P. falciparum Svenzea flava, exhibited strong inhibitory activity against strains in all five (Streptomyces IC S. purpurea and American sleeping sickness or Chagas disease (caused by Trypanosoma (T.) cruzi as well as African sleeping sickness (caused by T. brucei rhodesiense and T. brucei gambiensie), and American sleeping sickness or Chagas disease (caused by T. cruzi).
As shown in Table 1, two reports described two antitrypanosomal marine chemicals (95, 96) as well as their mechanisms of action. Oli and colleagues examined the mode of action of plakortide E (95), isolated from the sponge Plakortis halichondrioides, and demonstrated that it inhibited activity of *T. brucei* by a non-competitive, covalent or “mechanisms leading to slow-binding”, reversible inhibition of the parasite’s enzyme rhodesain [95]. Santos and colleagues extended the pharmacology of guanidine and pyrimidine alkaloids from the Brazilian marine sponge *Monanchora arbuscula*, and reported that batzelladine L (96) affected both trypomastigotes of *T. cruzi* and *L. infantum* promastigotes, demonstrating that several mechanisms including altered plasma membrane permeability, mitochondrial membrane depolarization, and increased reactive oxygen species, probably contributing to “parasite cell death” [96].

As shown in Table 1 and Figure 1, eleven additional marine natural products (97–107) exhibited antileishmanial and antiprotozoal activity, although their mechanisms of action remained undetermined. Abdelmohsen and colleagues reported that a new O-glycosylated angucycline actinosporin A (97), isolated from a culture of *Actinokineospora* sp. strain EG49 cultivated from a Red sea sponge *Sphicospesia vagabunda*, moderately inhibited the growth of *T. brucei brucei* [97]. Thao and colleagues isolated the terpenoid astroleptenol A (98) from a Vietnamese marine sea star *Astropecten polyacanthus*, and observed significant activity against *T. cruzi* and *T. brucei brucei* [98]. Viegelmann and colleagues identified a new saringosterol derivative (99) from the Irish marine sponge *Haliclona simulans*, which demonstrated antitrypanosomal activity against *T. brucei brucei* [99]. Using genome-directed lead discovery, Schulze and colleagues contributed a novel polyene macrolactam lobsomamide A (100) from a marine actinobacterium *Micronospora* sp. that was highly active towards the parasite *T. brucei brucei*, “likely via a parasite-specific mechanism” that remained undetermined [100]. Thao and colleagues assessed the emembranoid diterpenes lobocrasol A and C (101, 102), and crassumols D and E (104, 105), isolated from several Vietnamese soft corals, and noted that they displayed potent activity against *L. donovani* amastigotes and *T. brucei rhodesiense*, respectively [90]. Nakashima and colleagues found a new cyclopentadecane antibiotic mangromicin A (103) separated from the culture broth of the fungus *Lechevalieria aerocolonigenes* K10-0216 isolated from a Japanese mangrove sediment with potent activity against *T. brucei brucei* strain GUTat 3.1 [101]. Yang and colleagues characterized a new scalarane seseterpene sesterstamide (106) isolated from the Paracel islands marine sponge *Hyrtios* sp. that moderately inhibited *L. donovani* promastigotes [102]. Von Salm and colleagues contributed a novel tricyclic sesquiterpenoid shagene A (107) from an “undescribed” soft coral collected from the “Scotia Arc in the Southern Ocean” that was moderately active against *L. donovani* [103].

Drug-resistant strains of the intracellular pathogen *Mycobacterium tuberculosis* have stimulated a search for novel drug leads with novel mechanisms of action, and, as shown in Table 1 and Figure 1, five novel marine natural products (108–112) isolated from sponges and fungi evidenced promising activity, and thus contributed to the ongoing global search for novel antituberculosis agents during 2014–2015.

Arai and colleagues identified a novel aaptamine class alkaloid, 2-methoxy-3-oxoaaptamine (108), from a marine sponge *Aaptos* sp. that demonstrated strong inhibitory activity against *M. smegmatis* in “both active growing and dormancy-inducing hypoxic conditions” [104]. Daletos and colleagues isolated cyclic peptides callyaerins A and B (109, 110), from the Indonesian sponge *Callyspongia aerizusa*, that demonstrated potent antibacterial activity against *M. tuberculosis*, highlighting the “potential of these compounds as promising anti-TB agents” [105]. Kumar and colleagues established that a new diarylpyrrole alkaloid denigrin C (111) from an extract of the Indian marine sponge *Dendrilla nigra* exhibited strong *M. tuberculosis* H$_3$Rv activity “with a probable novel mechanism needed for antitubercular drug design … ” [106]. Lin and colleagues characterized a racemic, prenylated polyketide dimer, oxazinin A (112) from a filamentous fungus isolated from the Papua New Guinea ascidian *Lissoclinum putella*, which showed activity against *M. tuberculosis* with modest activity towards human transient receptor potential channels [107].
2.4. Antiviral Activity

As shown in Table 1 and Figure 1, twenty-one reports were published during 2014–2015 on the antiviral pharmacology of marine natural products (113–132) against human enterovirus 71, human cytomegalovirus, human immunodeficiency virus type-1 (HIV-1), human herpes simplex virus (HSV), influenza virus, hepatitis B virus, murine norovirus, respiratory syncytial virus (RSV), and sindbis virus.

As shown in Table 1, five reports described antiviral marine chemicals and their mechanisms of action. González-Almela and colleagues extended the pharmacology of pateamine A (113), isolated from the marine sponge Mycale sp. by demonstrating that the compound affected the translation of genomic and subgenomic mRNAs from Sindbis virus, although “subgenomic mRNA translation (was) more resistant to pateamine A inhibition” [108]. León and colleagues identified absyssomicin 2 (114) from a marine-derived actinobacterium Streptomycyes sp. that reactivated human immunodeficiency virus type-1 (HIV-1) by a protein kinase C and histone deacetylase-independent mechanism that “remains to be elucidated” [109]. Karadeniz and colleagues reported that the anti-HIV activity of the phlorotannin derivative 8,4′’-dieckol (115) from the Korean brown alga Ecklonia cava included the “ability to act against drug-resistant HIV-1 strains” by a mechanism that involved inhibition of cytopathic effects, as well as inhibition of HIV-1 reverse transcriptase enzyme [110]. Zhao and colleagues established that truncateol M (116) isolated from a culture of the sponge-associated fungus Truncatella angustata demonstrated potent activity against influenza A infections by a mechanism that targeted the virion assembly and release step, putatively becoming “a model structure of antiviral lead for further modification” [111]. Chen and colleagues determined that the alkaloid neoechinulin B (117) isolated from the marine-derived fungus Eurotium rubrum showed potent inhibition of H1N1 influenza A virus by binding to the influenza virion envelope hemagglutinin, thus “disrupting its interaction with the sialic acid receptor” on host cells [112].

An additional 15 marine natural products (118–132), listed in Table 1 and shown in Figure 1, demonstrated antiviral activity, but the mechanism of action of these compounds remained undetermined at the time of publication. Li and colleagues isolated a novel khayanolide, thaxylomolin I (118) from the seeds of the Trang (South Thailand) mangrove plant Xylocarpus moluccensis, which inhibited potent activity against influenza virus strain H1N1 [113]. Chen and colleagues contributed a new prenylated dihydroquinolone derivative 22-O-(N-Me-L-valyl)-21-epi-aflaquinolone B (119), produced by the mycelia of an Aspergillus sp. fungus derived from a South China Sea gorgonian Muricella abnormaliz, that inhibited respiratory syncytial virus influenza A virus H1N1 “with a high therapeutic ratio” [114]. Nong and colleagues found that two novel lactones territrem D and arisugacin A (120, 121) from a fungus Aspergillus terreus SC5GAR0162 derived from a South China sea gorgonian Echinogorgia aurantica exhibited potent HSV-1 activity “under non-cytotoxic concentrations” [115]. Li and colleagues isolated a novel isoindolinone-type alkaloid chartarutine B (122) from the marine sponge-associated fungus Stachybotrys chartarum, which displayed moderate inhibitory activity HIV-1, noting that “side chain variation directly affected the inhibitory effects” [116]. Gupta and colleagues purified debromoaplysiatoxin (123) from the marine Singaporan cyanobacterium Trichodesmium erythraeum, which inhibited Chikungunya virus with “minimal cytotoxicity”, and probably targeted the viral replication cycle after “viral entry” [117]. Pardo-Vargas and colleagues reported that the new diterpene dolabelladienol A (124) isolated from the Brazilian marine brown alga Dictyota paffii had potent activity against HIV-1 and, owing to “low cytotoxicity”, appeared to be a “promising anti-HIV-1 agent” [118]. Cheng and colleagues noted that one of the dolastane diterpenes isolated from the South China sea brown alga Dictyota pleciens, namely 13-deacetoxymijedictyol (125), showed inhibitory activity against wild-type HIV-1 replication, thus proposing that “Dictyota algae may be a potential source of antiviral lead compounds” [119]. Yamashita and colleagues investigated the effect of two polybrominated diphenyl ethers (22, 23) isolated from the Indonesian marine sponge Dysidea granulosa on the hepatitis B virus (HBV) core promoter activity, as well as the production of HBV DNA, suggesting that they may become “candidate lead compounds for the development of anti-HBV drugs” [120].
Cao and colleagues discovered that a new steroid echrebrosteroid C (126) from the South China sea gorgonian *Echinogorgia rebekka* evidenced high activity against respiratory syncytial virus, a common cause of lower respiratory tract disease in infants and children, as well as a high therapeutic index, thus “suggesting it might be useful as a potential antiviral agent” [121]. Jia and colleagues showed that one of two enantiomeric dimers, namely (+)-pestaloxazine A (127), isolated from a *Pestalotiopsis* sp. fungus derived from a soft coral, showed potent antiviral activity towards enterovirus 71, a small, single-stranded RNA virus that may cause hand, foot, and mouth disease associated with neurological complications in children and infants [122]. Eom and colleagues evaluated phlorofucofuroeckol-A (10), isolated from the edible brown alga *Eisena bicyclus* against murine norovirus, a leading cause of gastroenteritis, noting that, because of its strong anti-norovirus activity and high therapeutic index, it appeared “phlorotannins could be used as a potential source of natural antiviral agents” [123]. Cheng and colleagues discovered a new seco-cembranoid secocrassumol (128) from the marine soft coral *Lobophytum crassum*, which showed significant activity against human cytomegalovirus, a common herpesvirus infection in humans [124]. Using ligand-based pharmacophore mapping, Dineshkumar and colleagues demonstrated that the polycyclic macrolide sporolide B (129) isolated from the marine actinomycete *Salinispora tropica* showed significant inhibition of the HIV-1 reverse transcriptase, and thus “could be a possible drug candidate for HIV” [125]. Shin and colleagues isolated two new depsipeptides stellettapeptins A and B (130, 131) from an extract of the Australian marine sponge *Stelleta* sp. with significant HIV-inhibitory properties, suggesting that “this class of peptides may hold promise as anti-HIV agents” [126]. Sun and colleagues characterized a new tetramic acid derivative trichobotrysin A (132) isolated from the culture of South China sea *Trichobotrys effus* DFFSCS021 that inhibited herpes simplex virus type-1, responsible for lifelong oral infections in humans [127].

2.5. Anthelmintic Activity

As shown in Table 1, only one report was published during 2014–2015 on the anthelmintic pharmacology of marine natural products. Farrugia and colleagues isolated a 6-N-acyladenine alkaloid, phorioadenine A (133), from the southern Australian marine sponge *Phoriospongia* sp., which displayed “… nematocidal activity against *H. contortus* … slightly weaker than commercial anthelmintics levamisole and closantel”, perhaps suggesting that this compound may become a promising lead compound for the development of new anthelmintics [128].

3. Marine Compounds with Antidiabetic and Anti-Inflammatory Activity, and Affecting the Immune and Nervous System

Table 2 presents the 2014–2015 preclinical pharmacology of marine chemicals (134–218), which demonstrated either antidiabetic or anti-inflammatory activity, as well as affected the immune or nervous system, and whose structures are depicted in Figure 2.
Table 2. Marine pharmacology in 2014–2015: marine compounds with antidiabetic and anti-inflammatory activity, and affecting the immune and nervous system.

| Drug Class          | Compound/Organism ** | Chemistry     | Pharmacological Activity                                                                 | IC$_{50}$ b | MMOA c | Country d | References |
|---------------------|----------------------|---------------|-------------------------------------------------------------------------------------------|-------------|--------|-----------|------------|
| Antidiabetic        | fucoxanthin and fucoxanthinol (134, 135)/algae | Terpenoid f   | Improved glucose tolerance in vitro and in vivo                                           | 50 µM *     | Cytokine inhibition | JPN, S. KOR | [154,155] |
| Antidiabetic        | octaphloethol A (136)/algae | Shikimate h   | α-glucosidase inhibition                                                                 | 110 µM      | Molecular docking on active site | CAN, S. KOR | [156] |
| Antidiabetic        | phlorofucofuroeckol-A (10)/algae | Polyketide d  | Decreased glucose levels in vivo                                                         | 10 mg/kg ** | α-glucosidase inhibition | S. KOR | [157] |
| Antidiabetic        | Conv-Ins G1 (137)/cone snail | Peptide d     | Hypoglycemia induction                                                                  | 65 mg/g *   | Underdetermined | AUS, DNK, USA | [158] |
| Antidiabetic        | dehydroeuryrspongin A (138)/sponge | Terpenoid f   | PTP1B inhibition                                                                       | 3.58 µM     | Underdetermined | IDN, JPN | [159] |
| Antidiabetic        | Epicoecum sp. diterpene (139)/fungus | Terpenoid f   | α-glucosidase inhibition                                                                | 4.6 µM      | Underdetermined | CHN | [160] |
| Antidiabetic        | suncheonoside A (140)/bacterium | Terpenoid f   | Adiponectin production                                                                  | 10 µM *     | Underdetermined | S. KOR | [161] |
| Antidiabetic        | terrelumarmide A (141)/fungus | Peptide g     | Adiponectin production                                                                  | 37 µM *     | Underdetermined | S. KOR | [162] |
| Antidiabetic        | X. testudinaria lipid (142)/sponge | Polyketide d  | PTP1B inhibition                                                                       | 5.3 µM      | Underdetermined | CHN | [163] |
| Anti-inflammatory   | aclyonolide congeners (143, 144)/soft coral | Terpenoid f   | Macrophage NO inhibition                                                                | 2 µM *      | iNOS expression inhibition | JPN | [164] |
| Anti-inflammatory   | astaxanthin (145)/algae | Terpenoid f   | Oxidative stress inhibition in vivo                                                      | 10 µg/kg ** | CAT and SOD enhancement | CHN | [165] |
| Anti-inflammatory   | 8,8′-bieckol (146)/algae | Polyketide e  | Macrophage NO and PGE$_2$ release inhibition                                            | 50 µM *     | Inhibition of NFκB | S. KOR | [166] |
| Anti-inflammatory   | convolutamytidine A (147)/bryozoan | Alkaloid f | Formalin-induced licking behavior inhibition                                              | 0.01 mg/kg * | TNF-α, IL-6 release inhibition | BRA | [167] |
| Anti-inflammatory   | capgermacrene A (148)/soft coral | Terpenoid f   | Macrophage NO and IL-1β inhibition                                                       | <10 µg/mL * | Inflammation cytokine inhibition | MYS, S. KOR | [168] |
| Anti-inflammatory   | cathelicidin (4)/sea snake | Peptide f     | Binding of LPS to TLR4 inhibition                                                       | 4 µg/mL *   | Inflammation cytokine inhibition | CHN | [26] |
| Anti-inflammatory   | dactyloditerpenol acetate (149)/sea hare | Terpenoid f   | LPS-activated microglia in vitro inhibition                                              | 0.4–1 µM    | O$_2$- and TBXβ inhibition | USA | [169] |
| Anti-inflammatory   | dieckol (150)/algae | Shikimate h   | Macrophage iNOS transcription inhibition                                                | 30 µM *     | Inhibition of NFκB and p38MAPK | S. KOR | [170] |
| Anti-inflammatory   | dieckol (150)/algae | Shikimate h   | Macrophage iNOS and COX-2 transcription inhibition                                        | 12.5 µM *   | STAT1 phosphorylation inhibition | S. KOR | [171] |
| Anti-inflammatory   | excavatalol B (151)/gorgonian | Terpenoid f   | Macrophage iNOS and COX-2 transcription inhibition                                        | 25 µg *     | In vivo iNOS protein expression reduction | TWN | [172] |
| Anti-inflammatory   | flexibilide (152)/soft coral | Terpenoid f   | Neuropathic pain inhibition                                                              | 10 µg *     | Upregulation of TGF-β1 | TWN | [173] |
| Anti-inflammatory   | fucoxanthinol (135)/algae | Terpenoid f   | Macrophage TNF-α and MCP-1 release inhibition                                            | 10 µM       | COX-2 expression inhibition | JPN | [155] |
| Anti-inflammatory   | H. fusiforme flavone (153)/algae | Shikimate h/| Macrophage NO and PGE$_2$ release inhibition                                            | 10 µg/mL *  | iNOS, COX-2 expression inhibition | S. KOR | [174] |
| Anti-inflammatory   | 5β-hydroxyprolansadine B (154)/algae | Terpenoid f   | Macrophage NO release inhibition                                                        | 17 µM       | Partial iNOS expression inhibition | LKA, MYS, S. KOR | [175] |
| Anti-inflammatory   | glaucumolides A and B (155, 156)/soft coral | Terpenoid f   | Neutrophil SOX and elastase inhibition                                                  | 2.8–4 µM * | iNOS, COX-2 inhibition | TWN | [176] |
| Anti-inflammatory   | phlorofucofuroeckol-B (157)/algae | Polyketide d  | Microglia activation inhibition                                                         | 0.1 µg/mL * | InNOS, COX-2 inhibition | S. KOR | [177] |
### Table 2. Cont.

| Drug Class       | Compound/Organism ** | Chemistry   | Pharmacological Activity                                      | IC$_{50}$ b | MMOA c | Country d | References |
|------------------|----------------------|-------------|---------------------------------------------------------------|-------------|---------|-----------|------------|
| Anti-inflammatory | P. palmata lipid (158)/algae | Polyketide  | Macrophage NO release inhibition                              | 16.7 µM     | iNOS e  | CAN [178] |            |
| Anti-inflammatory | reduced scytosmine (159)/algae | Alkaloid    | Macrophage NO release inhibition                              | 1 µM *      | HO-1 f  | IPN [179] |            |
| Anti-inflammatory | sinulaptenolide A (160)/soft coral | Terpenoid   | LPS-activated rat microglia in vitro inhibition                | 0.5–2.9 µM  | Cytokine release inhibition | ESP, FIN, IND, ITA, [180] |
| Anti-inflammatory | sarcopanol A (161)/soft coral | Terpenoid   | iNOS, COX-2, and ICAM-1 transcription inhibition              | 8.3 µM      | NFXB b  | S. KOR, VNM [181] |
| Anti-inflammatory | sinomaximol H (162)/sponge | Terpenoid   | iNOS and ICAM-1 transcription inhibition 1 µM *               | 1.1 µM      | iNOS and PTP1B inhibition | VNM, S. KOR [182] |
| Anti-inflammatory | tanzawaic acid A (163)/fungus | Polyketide  | NO inhibition                                                 | 7.1 µM      |         | CHN, USA [184] |
| Anti-inflammatory | aspertetranone D (164)/fungus | Terpenoid   | IL-6 inhibition                                               | 40 µM *     |         | TWN [185] |
| Anti-inflammatory | briairenilide J (165)/soft coral | Terpenoid   | Neutrophil SOX and elastase inhibition 10–15 µM              | Undetermined|         | TWN [186] |
| Anti-inflammatory | briairenilides K and L (166, 167)/soft coral | Terpenoid   | Macrophage iNOS inhibition >10 µg/mL *                        | Undetermined|         | TWN [187] |
| Anti-inflammatory | briairenilides U, V, W (168, 169)/soft coral | Terpenoid   | Macrophage COX-2 and iNOS expression inhibition              | >10 µg/mL * |         | TWN [188] |
| Anti-inflammatory | briairenilides E and I (170, 171)/soft coral | Terpenoid   | Neutrophil SOX and elastase inhibition >10 µg/mL *           | Undetermined|         | TWN [189] |
| Anti-inflammatory | dermaczone H (172)/bacterium | Alkaloid    | Radial scavenging activity 18.8 µM                          | Undetermined|         | DEU, EGY, UK [190] |
| Anti-inflammatory | dysfrigalone A (173)/sponge | Terpenoid   | Macrophage NO release inhibition 6.6 µM                     | Undetermined|         | CHN [191] |
| Anti-inflammatory | D. plectens xenicane (174)/algae | Terpenoid   | Macrophage NO release inhibition 10 µM                       | Undetermined|         | CHN [192] |
| Anti-inflammatory | comaparvin (175)/crinoid | Polyketide  | Carrageenan-induced hyperalgesia inhibition 30 mg/kg *      | iNOS expression inhibition | TWN [193] |
| Anti-inflammatory | hirsutalin N and S (176, 177)/soft coral | Terpenoid   | Neutrophil elastase inhibition 10 µM *                        | Undetermined|         | TWN [194] |
| Anti-inflammatory | hirsutocapsin A (178)/soft coral | Terpenoid   | Neutrophil SOX and elastase inhibition 3.7–4.1 µM           | Undetermined|         | TWN [195] |
| Anti-inflammatory | isosuluflexiolide K (179)/soft coral | Terpenoid   | Macrophage COX-2 and iNOS expression inhibition              | >10 µM *    |         | TWN [196] |
| Anti-inflammatory | kyllinacceroid F (180)/soft coral | Terpenoid   | Neutrophil SOX and elastase inhibition 0.34 µM              | Undetermined|         | TWN [197] |
| Anti-inflammatory | krempfilinin N (181)/soft coral | Terpenoid   | Neutrophil SOX and elastase inhibition >10 µM *              | Undetermined|         | TWN [198] |
| Anti-inflammatory | krempfilins Q and R (182, 183)/soft coral | Terpenoid   | Neutrophil SOX and elastase inhibition >10 µM *              | Undetermined|         | TWN [199] |
| Anti-inflammatory | methylfarnesylquinone (184)/algae | Shikimate  | Neutrophil SOX and elastase inhibition 0.2–0.48 µg/mL       | Undetermined|         | TWN [200] |
| Anti-inflammatory | monanchosterol B (185)/sponge | Terpenoid   | Macrophage IL-6 expression inhibition 5 µM                   | Undetermined|         | S. KOR [201] |
| Anti-inflammatory | P. nodosus sterol (186)/starfish | Terpenoid   | IL-12 and IL-6 inhibition 1.3–3.1 µM                        | Undetermined|         | VNM, S. KOR [202] |
| Anti-inflammatory | rhitydione C (187)/fungus | Polyketide  | Macrophage NO inhibition 0.31 µM                            | Undetermined|         | THA [203] |
| Anti-inflammatory | sarcocrossolide E (188)/soft coral | Terpenoid   | Macrophage COX-2 and iNOS expression inhibition <10 µM *   | Undetermined|         | TWN [204] |
| Anti-inflammatory | sinulacembranolide A (189)/octocoral | Terpenoid   | Macrophage iNOS expression inhibition <10 µM                | Undetermined|         | TWN [205] |
| Drug Class            | Compound/Organism ** | Chemistry | Pharmacological Activity                                                                 | IC₅₀ b   | MMOA c   | Country d | References |
|-----------------------|----------------------|-----------|------------------------------------------------------------------------------------------|----------|----------|-----------|------------|
| Anti-inflammatory     | thromimarine B (190)/fungus | Terpenoid f | Macrophage NO inhibition                                                                  | >10 μM   | Undetermined | RUS, VNM  | [206]      |
| Anti-inflammatory     | tortuosene A (191)/soft coral | Terpenoid f | Neutrophil SOX inhibition                                                                 | 7.3 μM   | Undetermined | TWN       | [207]      |
| Immune system         | grassypeptolide A (192)/cyanobacterium | Peptide 8 | IL-2 and T-cell proliferation inhibition                                                   | 1 μM *   | Undetermined | CHN, JPN, USA | [208]     |
| Immune system         | F. reticulata alkaloids (193)/sponge | Alkaloid 8 | IL-2 inhibition                                                                           | 5–50 μM * | Undetermined | CHN, NLD  | [209]      |
| Immune system         | luzonicoside A (194)/starfish | Terpenoid f | Macrophage NO and ROS stimulation                                                         | 0.01–0.1 μM * | Undetermined | RUS, VNM  | [210]      |
| Immune system         | typicoside C1(195)/sea cucumber | Terpenoid f | Macrophage ROS stimulation                                                                | <1 ng/mL * | Undetermined | IND, RUS  | [211]      |
| Nervous system        | aurone glycoside (196)/fungus | Shikimic acid 6/Polyketide 7/Polyketide 8/Aldol 8 | Oxidative stress neuroprotection                                                          | 1 μM *   | Apoptosis inhibition | CHN       | [212]      |
| Nervous system        | azaspiracid-1 (197)/alga | Polyketide 6/Aldol 8 | Peripherin-labelled neurite process                                                        | 15 nM *  | Peripherin isoform downregulation                                                           | NOR       | [213]      |
| Nervous system        | caulerpine (198)/alga | Alkaloid 8 | Antinociceptive activity                                                                    | 40 mg/kg * | BRA       | [214]      |
| Nervous system        | 6-bromohypaphorphone (199)/sea slug | Alkaloid 8 | Human α7 nAChR agonist                                                                    | 23 μM    | RUS       | [215]      |
| Nervous system        | piscidin (200)/fish | Peptide 8 | Antinociceptive activity                                                                    | 20 μg/rat * | Phosphor-mTOR inhibition                       | TWN       | [216]      |
| Nervous system        | C. marmoratus conotoxin Mr1.7 (201)/cone snail | Peptide 8 | Ach-evoked membrane current inhibition                                                   | 53.1 nM  | A3JL2 nAChR inhibition                           | CHN       | [217]      |
| Nervous system        | C. littoratus conotoxin Lt6a (202)/cone snail | Peptide 8 | Neuronal Na⁺ current inhibition                                                           | 1 μM *   | Undetermined | CHN       | [218]      |
| Nervous system        | C. vitulinus peptide (203)/cone snail | Peptide 5 | Neuronal BK channel inhibition                                                             | 8.5 μM   | Electrostatic interaction with β4 subunits        | CHN, USA  | [219]      |
| Nervous system        | echinocchrome A (204)/sea urchin | Polyketide 4 | Acetylcholinesterase inhibition and NO scavenging                                         | 16.4 μM  | S. KOR, RUS | [220]      |
| Nervous system        | ganglioside LLG-3 (205)/starfish | Glycolipid | Neurogenesis stimulation in vitro                                                           | 1 nM *   | JPN, RUS  | [221]      |
| Nervous system        | heteronemin (206)/sponge | Terpenoid f | TDP-43 binding to DNA inhibition                                                            | 10.1 nM  | ITA       | [222]      |
| Nervous system        | pinnatoxin A (207)/mollusc | Polyketide 7/Aldol 8 | Muscle and neuronal nAChRs receptor inhibition                                             | 0.086–47.5 nM | FRA, USA  | [223]      |
| Nervous system        | PhcrTx1 (208)/sea anemone | Peptide 6 | ASIC inhibition                                                                           | 100 nM   | BEL, BRA, CUB, DEU, ESP, MEX | [224]      |
| Nervous system        | phlorofucofuroeckol-A (10)/alga | Polyketide 4 | Butyrylcholinesterase inhibition                                                           | 0.95 μM   | S. KOR       | [225]      |
| Nervous system        | S. auritum ceramicide (209)/soft coral | Polyketide 4 | Anoxiolytic and CNS depressing activity in vivo                                            | 1 mg/kg ** | EGY, USA | [226]      |
| Nervous system        | spirolide C (210)/dinoflagellate | Polyketide 5/Aldol 8 | nAChR inhibition                                                                           | 1.5–3 nM * | FRA       | [227]      |
| Nervous system        | zonanol (211)/alga | Meroterpenoid | Glutamate toxicity inhibition in vitro                                                     | 0.22 μM  | Nrf2/ARE pathway activation                     | JPN, USA  | [228]      |
| Drug Class       | Compound/Organism** | Chemistry       | Pharmacological Activity                      | IC_{50}^b | MMOA^c | Country^d | References |
|------------------|---------------------|-----------------|-----------------------------------------------|-----------|---------|-----------|------------|
| Nervous system   | aplysinellamide-1 (212)/sponge | Alkaloid       | ApoE secretion modulation                      | 30 µM *    | Undetermined | AUS, CAN | [229] |
| Nervous system   | A. terreus lactones (120, 121)/fungus | Polyketide ^d  | Acetylcholinesterase inhibition                | 4.2 µM     | Undetermined | CHN       | [115] |
| Nervous system   | C. araneous ar3j conotoxin (213)/cone snail | Peptide #      | Sleep induction                                 | 2 nM *     | Undetermined | IND       | [230] |
| Nervous system   | D. cepii steroid (214)/fungus | Terpenoid ^f   | Amyloid β-42 production inhibition             | 10 µM *    | Undetermined | DEU, FRA  | [231] |
| Nervous system   | genuarine (215)/cone snail | Alkaloid ^g    | Paralysis in vivo                               | 40 nM *    | Undetermined | PRT, USA  | [232] |
| Nervous system   | homoaoetin (216)/sponge | Alkaloid ^g    | Acetylcholinesterase inhibition                | 2.9–6.2 µM | Undetermined | THA       | [233] |
| Nervous system   | mooreamide A (217)/bacterium | Polyketide ^d  | CB1 binding                                    | 0.47 µM **  | Undetermined | ITA, PNG, USA | [234] |
| Nervous system   | S. spinosulus hydroquinone (218)/sponge | Shikimate ^h/Polyketide ^d | Enhance glutamate and ACh release | 10 µM *    | Undetermined | ITA       | [235] |

* Organism: Kingdom Animalia: fish (Phylum Chordata); bryozoan; coral and sea anemone (Phylum Cnidaria); crinoid, sea urchin, starfish (Phylum Echinodermata); cone snail, sea slug (Phylum Mollusca); sponge (Phylum Porifera); Kingdom Fungi: fungus; Kingdom Plantae: alga; Kingdom Monera: bacterium; Kingdom Protozoa: dinoflagellates; IC_{50}: concentration of a compound required for 50% inhibition, *: apparent IC_{50}, **: in vivo study; K_{i}: concentration needed to reduce the activity of an enzyme by half; MMOA: molecular mechanism of action; Country: AUS: Australia; BEL: Belgium; BRA: Brazil; CAN: Canada; CHN: China; CUB: Cuba; DEU: Germany; DNK: Denmark; EGY: Egypt; ESP: Spain; FIN: Finland; FRA: France; IDN: Indonesia; IND: India; ITA: Italy; JPN: Japan; LKA: Sri Lanka; MEX: Mexico; MYS: Malaysia; NLD: Netherlands; NOR: Norway; PNG: Papua New Guinea; PRT: Portugal; RUS: Russian Federation; S. KOR: South Korea; THA: Thailand; TWN: Taiwan; VNM: Vietnam; Chemistry: Polyketide; Terpene; Nitrogen-containing compound; Shikimate. Abbreviations: Ach: acetylcholine; ApoE: apolipoprotein E; ASIC: acid-sensing sodium ion channel; CAT: catalase; CB1: cannabinoid receptor 1; CNS: central nervous system; COX: cyclooxygenase; HO-1: heme oxygenase-1; ICAM: intercellular adhesion molecule-1; IL: interleukin; iNOS: inducible nitric oxide synthase; Kv current: voltage-gated K^+ current; MAPK: mitogen-activated protein kinase pathway; MDC/CCL2: macrophage-derived chemokine, C–C motif chemokine 22; nAChR: nicotinic acetylcholine receptor; NA: not available; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; Nrf2-ARE: nuclear transcription factor E2-related factor antioxidant response element; PTP1B: tyrosine protein phosphatase 1B; ROS: reactive oxygen species; SOD: superoxide dismutase; SOX: superoxide; STAT1: signal transducer and activator of transcription1; TDP-43: trans-activation response DNA-binding protein of 43 kDa.
Figure 2. Cont.
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3.1. Antidiabetic Activity

As shown in Table 2 and Figure 2, four publications reported on the mode of action of marine-derived antidiabetic compounds (10, 134–136). Kang and colleagues contributed to the pharmacology of diabetes by noting that the marine carotenoid fucoxanthin (134), isolated from the marine brown alga *Ishige okamurae*, protected cells and organs from oxidative damage induced by high glucose both in vitro and in vivo, concluding that “fucoxanthin may prove to be an effective mediator to control oxidative stress in hyperglycemia” [155]. Maeda and colleagues observed that fucoxanthin and its metabolite, fucoxanthinol (135), improved obesity-induced inflammation in adipocyte cells with concomitant suppression of tumor necrosis factor-α and monocyte chemotactic protein-1 RNA expression, thus concluding that fucoxanthin “ameliorates glucose tolerance in the diabetic mice model” [154]. Lee and colleagues reported that octaphlorethol A (136) isolated from the marine brown alga *Ishige foliacea* showed a potent anti-hyperglycemic effect in mice by potently binding to α-glucosidase, an enzyme that plays a role in blood glucose control, thus demonstrating its potential use “for treatment of type 2 diabetes mellitus” [156]. You and colleagues showed that the phlorotannin phlorofucofuroeckol-A (10) isolated from the brown alga *Ecklonia cava* alleviated postprandial hyperglycemia in diabetic mice by a mechanism that involved significant inhibition of α-glucosidase and α-amylase, thus proposing this natural product “as a nutraceutical for diabetic individuals” [157].

An additional six marine natural products (137–142), listed in Table 2 and shown Figure 2, demonstrated antidiabetic activity, but the mechanism of action of these compounds remained undetermined at the time of publication. Safavi-Hemami and colleagues described a specialized insulin Con-Ins G1 (137) used for chemical warfare by the fish-hunting cone snail *Conus geographus*, which appear to have “evolved to act rapidly and potently to cause severe hypoglycemia” [158].
Yamazaki and colleagues found that the sesquiterpene dehydroeuryspongin A (138) isolated from the Japanese marine sponge *Euryspongia* sp. inhibited the protein tyrosine phosphatase 1B, considered a key enzyme involved in type II diabetes and obesity because it plays a role in the dephosphorylation of insulin and leptin receptors [159]. Xia and colleagues contributed a new isopimarane diterpene (139) isolated from the culture of the fungus *Epicoccum* sp. associated with the marine sea cucumber *Apostichopus japonicus* that potently inhibited α-glucosidase [160]. Shin and colleagues isolated a new benzothioate glycoside suncheonoside A (140) from a Korean marine-derived *Streptomyces* strain that promoted adiponectin production during adipogenesis in vitro, thus “suggesting antidiabetic potential” [161]. You and colleagues reported that the lumazine-containing peptide terrelumamide A (141), isolated from the culture broth of the Korean marine-derived fungus *Aspergillus terreus*, improved insulin sensitivity and adiponectin production in an in vitro human adipogenesis model [162]. He and colleagues characterized a polyunsaturated lipid (142) from the Chinese marine sponge *Xestospongia testudinaria*, which was shown to inhibit protein tyrosine phosphatase 1B, considered as a significant target for the “treatment of type II diabetes and obesity” [163].

3.2. Anti-Inflammatory Activity

As shown in Table 2 and Figure 2, there was a remarkable increase in anti-inflammatory pharmacology of marine compounds (143–191) during 2014–2015. The molecular mechanism of action of marine natural products (143–163) was assessed in both in vitro and in vivo preclinical pharmacological studies in twenty-two papers that used several in vitro models: the murine RAW 264.7 macrophages, a human keratinocyte cell line, a human hepatocarcinoma HepG2 cell line, primary rat brain microglia, and a murine microglia BV-2 cell line.

Taira and colleagues evaluated the anti-inflammatory properties of alcyonolide and its congener (143, 144), isolated from the Okinawan soft coral *Cespitularia* sp. in lipopolysaccharide (LPS)-stimulated RAW264.7, observing inhibition of NO as well as gene expression of the proinflammatory genes inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 mRNA [164]. Guo and colleagues extended the pharmacology of the terpenoid astaxanthin (145) by reporting that a reduction of oxidative stress in an in vivo model of rat burn injury was concomitant with a decrease in the level of malondialdehyde, an indicator of lipid peroxidation, as well as an increase of antioxidant enzymes superoxide dismutase and catalase, a “protective effect” that held “potential as a new drug treatment of severely burned patients ...” [165]. Yang and colleagues reported that the polyketide 8,8′-bieckol (146), isolated from the edible marine brown alga *Ecklonia cava*, significantly inhibited both pro-inflammatory NO, prostaglandin E2 (PGE2), and interleukin 6 (IL-6) production, as well as gene expression by downregulating NF-κB signaling pathway and ROS accumulation in both LPS-stimulated primary macrophages and RAW 264.7 macrophages, thus demonstrating the compound’s “anti-inflammatory potential ... in systemic inflammatory conditions such as sepsis” [166]. Fernandes and colleagues studied convolutamydine A (147), isolated from marine bryozoan *Amathia convoluta*, and two synthesized analogs, and determined that they exhibited significant in vivo and in vitro anti-inflammatory activity by a mechanism that involved reduced leukocyte migration as well as inhibition of the production of the cytokine IL-6, PGE2, and NO [167]. Phan and colleagues isolated a new bicyclogermacrene capgermacrene A (148) from the Bornean soft coral *Capnella* sp. and observed significant in vitro inhibition of NO production by RAW 264.7 macrophages by inhibition of iNOS expression, proposing this compound as a “promising iNOS inhibiting agent” [168]. Jiménez-Romero and colleagues investigated the effect of the diterpene dactylopterpenol acetate (149) extracted from the Puerto Rican tropical sea hare *Aplysia dactylomela* on *E. coli* LPS-activated rat neonatal microglia in vitro, observing the potent inhibition of both thromboxane B2 and superoxide anion (O2−) generation, proinflammatory mediators associated with neuroinflammation, concluding that the data “support further development” of this compound [169]. Two studies extended the anti-inflammatory pharmacology of dieckol (150) isolated from the brown alga *Ecklonia cava*: Choi and colleagues demonstrated the compound inhibited LPS-induced iNOS expression by affecting mitogen-activated
protein kinases (MAPK), “significantly p38MAPK” in the mouse macrophage 264.7 cell line in vitro [170], while Kang and colleagues demonstrated that dieckol suppressed production of macrophage-derived chemokine, C–C motif chemokine 22, an inflammatory chemokine that controls leukocyte movements by down-regulating the activation of the signal transducer and activator of transcription (STAT)1 signaling pathway in human keratinocytes [171]. Lin and colleagues characterized the anti-inflammatory effects of the diterpene excavatolide B (151) isolated from the cultured Formosan marine gorgonian *Briareum excavatum* and observed that, in vitro, it inhibited iNOS and COX-2 mRNA expression in LPS-treated murine RAW 264.7 macrophages, while in vivo it attenuated carrageenan-induced rat paw inflammation and pain, thus concluding that “excavatolide B may serve as a useful therapeutic agent for the treatment of acute inflammation” [172]. Chen and colleagues investigated the antinociceptive properties of flexibilide (152), isolated from the Australian soft coral *Sinularia flexibilis* in the rat chronic injury model of neuropathic pain, observing significant analgesic effects concomitant with suppression of iNOS expression in microglia and astrocytes in the spinal dorsal horn, accompanied with upregulation of transforming growth-factor-β1 (TGF-β1), “suggesting involvement of TGF-β1 in the anti-neuroinflammatory and analgesic effects” [173]. Kim and colleagues reported that a polyhydroxyflavone (153) isolated from the marine alga *Hizikia fusiforme* suppressed LPS-stimulated RAW 264.7 cells’ release of pro-inflammatory cytokines, as well as both iNOS and COX-2 expression, by attenuating nuclear transcription factor-κB (NF-κB) translocation, and thus might become a “potential therapeutic agent for patients with, or at risk of, septic shock or other inflammatory diseases” [174]. Wijesinghe and colleagues evaluated 5β-hydroxypalisadin B (154), a brominated secondary metabolite isolated from the Malaysian marine red alga *Laurencia snackeyei*, on LPS-stimulated RAW 264.7 macrophages and observed significant reduction of several pro-inflammatory cytokines, NO, and PGE2 generation, and thus concluded that the compound might help development of “an active ingredient in pharmaceutical, nutraceutical… “ applications [175]. Huang and colleagues characterized two novel biscembranes glaucumolides A and B (155, 156) from the cultured soft coral *Sarcophyton glaucum* that significantly inhibited O2- generation and elastase release in human neutrophils, while also reducing expression of iNOS and COX-2 in LPS-treated murine RAW 264.7 macrophages, concluding that these two compounds “might be useful for future biomedical applications” [176]. Yu and colleagues determined that the effects of phlorofucofuroeckol-B (157), isolated from the marine alga *Ecklonia stolonifera*, on the decreased production of pro-inflammatory mediators by LPS-stimulated BV-2 microglia cells, as well as reduced COX-2 and iNOS expression, resulted from inhibition of the iκB-α/NF-κB and Akt/ERK/JNK pathways, thus proposing that this compound might be “considered as a therapeutic agent against neuroinflammation” [177]. Babskota and colleagues isolated a new phosphatidyglycerol (158) from an extract of the marine red alga *Palmaria palmata*, also commonly known as dulse, which strongly inhibited NO release from LPS treated murine RAW 264.7 macrophages, probably by a mechanism that down-regulated iNOS, thus suggesting that “consumption of dulse as a functional food may help to reduce inflammation associated with various diseases” [178]. Itoh and colleagues showed that reduced scytominin (159) isolated from the cosmopolitan colonial cyanobacterium *Nostoc commune* strongly inhibited LPS and interferon-γ-induced NO production in murine macrophage RAW 264.7 macrophages, by generating reactive oxygen species by activation of the phosphatidylinositol-3-kinase/Akt and the p38 mitogen-activated protein kinase/nuclear factor erythroid 2-related factor 2 signaling pathways [179]. Lillsunde and colleagues reported that a norcembranoid sinuleptolide (160) isolated from the Indian soft coral *Sinularia kavarattiensis* potently modulated both morphology and release of pro-inflammatory and anti-inflammatory mediators by LPS-treated rat primary microglial cells in vitro, thus decreasing microglia activation, which has been hypothesized to be involved in the “progression of chronic neurodegenerative diseases.. and central nervous system (CNS) homeostasis” [180]. Thao and colleagues contributed a new polyhydroxylated steroid sarcopanel A (161) from the Vietnamese soft coral *Sarcophyton pauciplicatum* that inhibited tumor necrosis factor (TNF)-α and interferon (IFN)γ-induced expression of COX-2, iNOS, and intercellular adhesion molecule-1 (ICAM-1) in the spontaneously transformed immortal human keratinocyte
cell line HaCaT via inhibition of NF-κB signaling pathway activation [181]. Thao and colleagues investigated the diterpenoid sinumaximol (162), isolated from the marine soft coral Sinularia maxima, and determined that it significantly inhibited TNF-α-induced NF-κB transcriptional activity in a human hepatocarcinoma HepG2 cell line, while concomitantly inhibiting the expression of pro-inflammatory iNOS and ICAM-1mRNA expression, thus supporting the “therapeutic potential as anti-inflammatory” of this compound [182]. Quang con colleagues determined that tanzawaic acid A (163), isolated from a marine fungus Penicillium sp. SF-6013 derived from the Pacific sea urchin Brisaster latifrons, inhibited both NO and PGE2 production from LPS-activated murine BV-2 microglia cells and RAW 264.7 murine macrophages, while suppressing iNOS and COX-2 expression and inhibiting protein tyrosine phosphatase 1B [183].

In contrast to the marine compounds (143–163) with described anti-inflammatory mechanisms of action described in the preceding paragraph, and as shown in Table 2, for marine compounds (164–191), only anti-inflammatory activity (IC_{50}) was reported, but the molecular mechanism of action of these marine-derived compounds remained undetermined at the time of publication: a new highly oxygenated meroterpenic asptetarotane D (164) isolated from the marine algal-associated fungus Aspergillus sp. ZL0-1b14 [184]; a novel 6,12-dichlorobriarene diterpenoid briarenolide J (165), two briarene diterpenoids briarenolides K and L (166, 167), and the briarenolides U–W (168–169), all compounds isolated from the Taiwanese octocoral Briareum sp. [185–187]; two new briarene diterpenoids briaviolides E and I (170, 171), isolated from the Taiwanese soft coral Briareum violaceae [188]; a new pigmented phenazine compound dermacozine H (172), isolated from the actinomycete Dermacoccus abyssi sp. nov. strain MT1.1, isolated from a Mariana Trench sediment at a depth of 10,898 m [189]; a novel sesquiterpene dysifragilone A (173), isolated from the South China Sea sponge Dysidea fragilis [190]; a new xenicane 4α-hydroxyxapaclyctolactone (174), isolated from a Chinese brown alga Dictyota plectens [191]; a polyketide comaparvin (175), isolated from the Taiwanese marine crinoid Comanthus bennetti [192]; two novel eunicellin-type diterpenoids hirsutalins N and S (176, 177) and a new tocopherol-derived metabolite hirsutocospiro A (178), isolated from the Taiwanese soft coral Cladiella hirsuta [193–195]; a new cembranoid isosinulaflexilide K (179), isolated from cultured Taiwanese soft corals Sinularia sandensis and Sinularia flexibilis [196]; a novel 9,11-secoergosteryl klyfllactisteroid F (180), isolated from the Taiwanese soft coral Klyxum flaccidum [197]; new eunicellin-type diterpenoids krempfielins N (181), Q (182), and R (183), isolated from a Taiwanese soft coral Cladiella krempfi [198,199]; a methylfarnesylequinone (184), isolated from the Taiwanese marine brown alga Homeostrichus formasana [200]; a new steroid monochasterol B (185), isolated from the Korean sponge Monanchora sp. [201]; a oxygenated steroid derivative (186), isolated from the Vietnamese starfish Protoreaster nodosus [202]; a new spirobisnaphthalene rhytidenone C (187), isolated from an extract of a cultured fungal endophyte Rhizidiyleron sp. AS21B isolated from a Thailandes mangrove area [203]; a known terpenoid sarcocasscolide E (188), isolated from a Taiwanese soft coral Sarcophyton crassoceaula [204]; a new cembrane diterpenoid sinulacembranolide A (189), isolated from the Taiwanese soft coral Sinularia gavelli [205]; a new eudesmane-type sesquiterpene thomimarine B (190), isolated from the fungus Penicillium thomii KMM 4667 isolated from the Japanese sea grass Zostera marina [206]; and a novel diterpenoid tortuosen A (191), isolated from the Taiwanese soft coral Sarcophyton tortuousum [207].

3.3. Marine Compounds with Activity on the Immune System

As shown in Table 2 and Figure 2, the preclinical pharmacology of marine compounds that affected the immune system showed a decline, as previously reported in this series.

Kwan and colleagues reported that the peptide grassypeptolide A (192), isolated from the marine cyanobacterium Lyngbya confervoides, inhibited IL-2 production and proliferation of activated T cells by inhibiting the protease dipeptidyl peptidase 8, probably by binding at inner cavity of the enzyme at two distinct sites [208]. Wang and colleagues isolated a pair of novel bisbeterocyclic quinolone-imidazole alkaloids (+)- and (-) spiroreticulatine (193) from the South China sea sponge...
**Fascaplysinosis reticulata**, which showed inhibition of IL-2 production by Jurkat T cells [209]. Kicha and colleagues determined that the cyclic steroid glycoside luzonicoside A (194), isolated from the starfish *Echinaster luzonicus*, potently enhanced lysosomal activity, ROS level elevation, and NO synthesis in RAW 264.7 murine macrophages, thus seeming “promising for further investigation as a potent immunomodulatory agent” [210]. Pislyagin and colleagues investigated a triterpene glycoside typicoside C1 (195), isolated from the sea cucumber *Actinocucumis typica*, and observed that it demonstrated strong immunostimulatory effect on ROS formation in mouse peritoneal macrophages in vitro, with concomitant low cytotoxicity [211].

### 3.4. Marine Compounds Affecting the Nervous System

As shown in Table 2 and Figure 2, in 2014–2015, the preclinical marine nervous system pharmacology of compounds (196–211) described several mechanism of action: at the nicotinic acetylcholine receptor and potassium channels, with conopeptides, and in models of antinociception and neuroprotection.

Four marine compounds were shown to bind nicotinic acetylcholine receptors (nACHR) (199, 207, 210) and potassium (K+) channels (208). Kasheverov and colleagues determined the effect of 6-bromohyaphorhine (6-BHP) (199), isolated from the marine nudibranch mollusk *Hermissonella crassicornis*, on different nACHR, demonstrating that, because 6-BHP competed with α-bungarotoxin for binding to the human α7 nACHR, it was the “first low-molecular weight compound from (a) marine source which (was) an agonist of the nACHR subtype” [215]. Bourne and colleagues conducted detailed studies to determine the molecular pharmacology of the macrocyclic imine phycotoxin pinnatoxin A (207), originally isolated from the digestive glands of the mollusk *Pincta attenuata*, towards neuronal α7nACHR, observing that the bicyclic EF-ketal ring was a novel binding determinant for mediating polar versus non-polar interactions, and thus is able to “confers nACHR subtype selectivity … (of) these prevalent marine biotoxins” [223]. Rodríguez and colleagues discovered a novel peptide PhcrTx1 (208) from the sea anemone *Phymanthus crucifer* that inhibited voltage-gated K+ ion channels, including acid-sensing ion channel (ASIC) (IC_{50} = 100 nM), and that would represent “the first member of a new structural group of sea anemone toxins acting on ASIC” [224]. Aráoz and colleagues extended the pharmacology of the “fast-acting” lipophilic marine toxin 13,19-desmethyl spirolide C (210), extracted from cultures of the dinoflagellate *Alexandrium ostenfeldii*, defining the mode of action and molecular targets using in vitro electrophysiological experiments, and thus showing that the toxin blocked human neuronal nACHR with high affinity, observations supported by molecular docking experiments “highlighting the nicotinic basis of the neurotoxicity of (this toxin) to mammalian peripheral and central nervous system” [227].

Three studies extended the pharmacology of conopeptides (201–203). Wang and colleagues discovered a novel α-conotoxin Mr1.7 (201) in the venom of the marine snail *Conus marmoreus* that inhibited α3β2, α9α10, and α6/α3β2β3 nACHR subtypes (IC_{50} = 53.1, 185.7, and 284.2 nM, respectively), noting that the PE residues at the N-terminal sequence of Mr1.7 were “important for modulating activity and selectivity” [217]. Zhou and colleagues reported the expression and sodium channel activity of peptide It16a (202), a novel framework XVI conotoxin from the M-superfamily isolated from the worm-hunting snail *C. litteratus*, and, using a variety of electrophysiological techniques, demonstrated that it preferentially inhibited voltage-gated Na+ channels (apparent IC_{50} = 1 μM) in mammalian sensory neurons, with the authors noting “It16a has similar function as μ-conotoxins” [218]. Li and colleagues extended the pharmacology of Vt3.1 conotoxin (203), isolated from the venom of the marine cone snail *C. vitulinus*, and demonstrated that it preferentially inhibited large conductance, voltage, and Ca2+ activated K+ (BK) channels containing the β4 subunit (IC_{53} = 8.5 μM), which appears to be present in brain and neuronal functions by a mechanism that required electrostatic interactions with the channel protein, making it an excellent tool “uniquely suited in neuroscience involving BK channels” [219].

Two studies reported marine compounds (198, 200) that contributed to nociceptive pharmacology. Cavalcante-Silva and colleagues assessed the mechanism involved in in vivo antinociception produced
by the bisindole alkaloid caulerpine (198), isolated from the marine alga Caulerpa, demonstrating that, in the in vivo murine writhing test, the effect was likely mediated by “pathways involving α2-adrenoceptors and 5-HT3 receptors”, thus proposing caulerpine as a possible “dual-action analgesic drug(s)” [214]. Chen and colleagues investigated the anti-neuropathic properties of the antimicrobial peptide piscidin (200) and observed that the compound demonstrated in vivo anti-nociceptive effects in a rat model of neuropathy by a signaling mechanism that suppressed up-regulation of interleukin-1 in microglia and phosphorylated mammalian target of rapamycin in astrocytes, concluding it “may have potential for development as an alternative pain-alleviating agent” [216].

The neuroprotective activity of marine compounds (196, 197, 205, 206, 211) was reported in five studies. Wu and colleagues observed that the novel (Z)-7,4′-dimethoxy-6-hydroxy-aurone-4-O-β-glucopyranoside (196) isolated from the endophytic fungus Penicillium citrinum of the mangrove Bruguiera gymnorrhiza derivative decreased 1-methyl-4-phenylpyridium-induced neurotoxicity in rat pheochromocytoma PC12 cells in vitro by a mechanism that elevated mitochondrial membrane potential, decreased DNA fragmentation, and inhibited apoptosis [212]. Hjornevik and colleagues completed an extensive in vitro “neurotoxicological” study with the marine algal toxin azaspiracid-1 (197) and observed rat PC12 cells’ differentiation-related morphological changes associated with the expression of the PC12-associated neuronal differentiation marker peripherin on neurite-like processes, suggesting this molecule “triggers a differentiation process” [213]. Yamagishi and colleagues explored the structure–activity relationship of LLG-3 (205), a ganglioside isolated from the starfish Linchia laevigata, and discovered that the methyl group at C8 of the terminal sialic acid residue was of critical significance for neuritogenic activity. Furthermore, detailed signaling studies revealed the “activation of mitogen-activated protein kinase signaling pathway” [221]. Cassiano and colleagues, using chemical proteomics, noted that the terpenoid heteronemin (206), isolated from the marine sponge Hyrtios sp., targeted TDP-43, a major component of inclusions that characterize amyotrophic lateral sclerosis and front-temporal lobar degeneration, by lowering its affinity “towards nucleic acids”, and thus becoming a “relevant chemical tool in the study of TDP-43 related processes” [222]. Shimizu and colleagues provided the “first report” that the pro-electrophilic sesquiterpenic zonarol (211), isolated from the Japanese brown alga Dictyopteris undulata, provided neuroprotection by activating the nuclear factor (erythroid-derived-2)-like 2/antioxidant responsive element Nrf2/ARE pathway, inducing phase-2 enzymes and providing oxidative stress protection to cerebrocortical neurons in vitro, concluding that the compound “represents a lead compound for the treatment of chronic neurodegenerative diseases associated with oxidative stress” [228].

As shown in Table 2, three marine compounds were shown to modulate other molecular targets, that is, γ-aminobutyric acid (GABA) receptor (209), and the acetylcholinesterase (204) and butyrylcholinesterase enzyme (10). Lee and colleagues discovered that the pigment echinochrom A (204), isolated from the sea urchin Scaphechinus, inhibited acetylcholinesterase (IC50 = 16.4 μM) by an irreversible and uncompetitive mechanism that might be useful in “treating acetylcholine-limited diseases”, such as Alzheimer’s disease and “other forms of dementia” [220]. Eltahawy and colleagues isolated of a new ceramide (209) from the Red sea soft coral Sarcophyton auritum, which demonstrated antiepileptic activity in vivo with a central nervous system depressing mechanism that appeared to involve “GABA receptor modulation rather than serotonin receptor inhibition” [226]. Choi and colleagues reported that the polyphenol phlorofucofuroeckol-A (10), isolated from the Korean brown alga Ecklonia cava, potently inhibited butyrylcholinesterase, a novel target for Alzheimer’s disease, suggesting that “phlorotannins … to be very promising medicinal compounds” [225].

In contrast to the marine compounds affecting the nervous system with investigated mechanisms of action discussed above, and as shown in Table 2, for marine compounds (120, 121, 212-218), only an IC50 was reported, but the molecular mechanism of action of these compounds remained undetermined at the time of publication: an Australian marine-sponge Aplysinella sp.-derived aplysinellamide-1 (212) [229], the novel lactones territrem D, and arisugacin A (120, 121) from a fungus Aspergillus terreus...
SCSGAF0162 derived from a South China sea gorgonian *Echinogorgia aurantiaca* [115]; an Indian marine cone snail *Conus araneus* ar3p peptide (213) [230]; a new steroid (214) from a fungus *Dichotomomyces cepii* isolated from an Australian marine sponge *Callyspongia cf. C. flamma* [231]; a novel genuaine (215) isolated from Cape Verde marine cone snail *Conus genuanus* [232]; a bromotyrosine alkaloid homoerothionin (216) isolated from the Thai sponge *Acanthodendrilla* sp. [233]; a new alkyl amide mooreamide A (217) from the Papua New Guinean marine cyanobacterium *Moorea boullonii* [234]; and a hydroxyoctaprenyl 1,4′-hydroquinone (218) isolated from the Italian marine sponge *Sarcotragus spinosulus* [235].

4. Marine Compounds with Miscellaneous Mechanisms of Action

The 2014–2015 preclinical pharmacology of 83 marine compounds (219–300) with miscellaneous mechanisms of action is shown in Table 3, with their corresponding structures presented in Figure 3. Because, at the time of publication, a comprehensive pharmacological characterization of these compounds remained unavailable, their assignment to a particular drug class will probably require further investigation.

As reported in the peer-reviewed literature, Table 3 presents the pharmacological activity, an IC$_{50}$, and a molecular mechanism of action of the following marine natural compounds: sea anemone *Aiptasia diaphana* toxic peptide AdE-1 (219) [236]; sponge alkaloid aaptamine (220) [237]; dinoflagellate *Amphidinium* sp. polyketide amphirionen-4 (221) [238]; algal terpenoid astaxanthin (145) [239]; sponge alkaloids bastadins 6 and 16 (222, 223) [240]; brown alga *Eisenia bicyclus* polyketide 6,6-bieckol (222) [241]; *Streptomyces* sp. strain CNH-287 alkaloid (-)-chlorizidine A (225) [242]; soft coral *Cladiella australis* dihydroaustrafusulione alcohol (226) [243, 244]; edible brown alga *Ishige okamurae* terpenoid diphlorethohydroxycarmelol (227) [245]; sea urchin *Scaphechinus mirabilis* alkaloid echinochrome A (204) [246, 247]; brown alga *Ecklonia stolonifera* polyketide eckoll (228) [248]; sponge derived fungus *Dichotomomyces cepii* terpenoid emindole SB (229) [249]; Arctic *Streptomyces nitrosporeus* YBH10-5 farnesylquinone (250) [250]; fungus *Stachybotrys longispora* FG216 pyrano indolome alkaloid fibrinolytic compound 1 (231) [251]; fungus *Paecilomyces formosus* formosusin A (232) [252]; brown alga *Ecklonia cava* phlorotannin fucodiphlorethol G (233) [253]; green alga *Spirogyra* sp. polyphenol gallic acid (234) [254]; cyanobacterium *Schizothrix* sp. gallinamide A (235) [255]; sponge *Stylissa aff. carteri* girolinne (236) [256]; sponge *Spongilla meleagris* terpenoids gracilins H, A, and L (237–239) [257]; new anemone *Heteractis crispa* Kunitz-type polypeptides HCRG1 and HCRG2 (240, 241) [258]; new sponge *Hyrtios* sp. sesterterpenoid 2 (242) [259]; sponge *Incinia ramose* inciniastatin A (243) [260]; ascidian *Eudistoma cf. rigida* polyketide lejimalide C (244) [261]; red alga *Laurencia brongniartii* brominated indole (245) [262]; sponge *Neopetrosia* sp. pyridine nucleoside neopetroside A (246) [263]; edible brown alga *Ecklonia stolonifera* phlorotannin chlorofucofuroeckol-A (10) [264]; sponge *Theonella swinhoei* peptide polytheonamide B (247) [265]; green alga *Conus fragile* terpenoid siphonaxanthin (248) [266]; deep-sea derived fungus *Spiorastis* sp. MCC3 A000308 spiroastaxine J and L (57, 249) [267]; bacteria *Thalassosira* sp. CNJ328 and *Tistrella bauzanensis* TIO7329 thalassospiramide C (250) [268]; mangrove fungus *Xylaria* sp. xyloketal B (251) [269, 270]; and sponge *Xestospongia testudinaria* brominated polyunsaturated lipid (252) [271].

Also consolidated in Table 3 is the pharmacological activity (IC$_{50}$ for enzyme or receptor inhibition) of marine-derived compounds (253–300), but the mechanism of action remained undetermined at the time of publication: a dinoflagellate *Dinophysis acuminata* new polyether macrolide acuminolide A (253) [272]; fungus *Alternaria alternata* alternariol derivatives (255–257) [136]; bacterium *Streptomyces* sp. linear peptide ahapatinin Ac (254) [273]; ascidian *Aplidium* sp. new dipeptide aplanamide D (258) [274]; fungi *Penicillium thomii* and *P. lividum* new meroterpenoids astalides 4 and 9 (259, 260) [275]; *Streptomyces axinellae* axinelline A (261) [276]; dinoflagellate *Karenia brevisulcata* polyether brevisulcatic acid-4 (262) [277]; green alga *Caulerpa racemosa* 4′,5′-dehydrodidiydrofytromyxine A (263) [278]; sponge *Dactylospanga metachromia* sesquiterpenes nakijiquinone N (264), nakijinol C (266), and known analog 18-hydroxy-5-epi-hyrtiophenol (265) [279]; ascidian *Didemnum* sp. siphoneketal dikemaketal D and E (267, 268) [280]; sponge *Dysidea avara* sesquiterpene dysiquinol D (269) [281]; brown alga *Laminaria
japonica terpenoid fucoxanthin (134) [282]; sponge Xestospongia testudinaria halenaquinol sulfate (270) [283]; sponge Xestospongia sp. halenaquinone derivative, 1-hydroxyethylhalenaquinone (271) [284]; sponge Stylissa massa and S. flabelliformis bromopyrrole alkaloids (272–274) [285]; sponge Callyspongia sp. hymenaldisine (275) [286]; sponge Hyattella sp. hyattellactone A (276) [287]; sponge Hippospongia lachne sesterterpene hippolide derivative (277) [288]; sponge Suberea ianthelliformis ianthelliformisamines A, B, and C (278, 7, 8) [289]; sponge Plakortis cfr. lita sterols incisterols A5 and A6 (279, 280) [290]; soft coral Lobophytum crispum embranoid diterpene 2,16:7,8,8S,8S-diepoxy 1,3,11,15-cembratetraene (281) [291]; red alga Laurencia okamurai laurenene-type sesquiterpenoid laurokamurane A (282) [292]; gorgonian Echinogorgia pseudossapo alkaloid malanganenone L (283) [293]; fungus Hansfordia sinuosae sesquiterpenoid punctaporonin K (284) [294]; fungus Aspergillus versicolor ZLN-60 cyclic peptide psychrophilin G (285) [295]; green alga Caulerpa racemosa bisindole alkalkoid racemosin C (286) [296]; red coral Lobophytum ehrenbergii prostaglandin derivative sarcoehrendin B (287) [297]; soft coral Sarcophyton trocheliophorum Marenzeller diterpene sarsolidile A (288) [298]; fungus Stachybotrys sp. HH1 ZSDS1F1-2 xanthone derivative stachybogrisephenone B (289) [299]; brown alga Sargassum thunbergii alkapolyene 1 (290) [300]; red alga Palmaria palmata mycosporine-like amino acid shinorine (291) [301]; soft coral Sinularia sp. cyclopentenone sinularone D (292) [302]; fungus Stachybotrys chartarum N-(2-benzenepropanoic acid) stachybotrylactam (293) [303]; sponge Petrosia corticata meroditerpenoids strongylophorine -13/-14 (294) [304]; sponge Theonella swinhoei steroid swinhoeisterol A (295) [305]; brown alga Sargassum thunbergii thunberol (296) [306]; sponge Xestospongia vansoesti meroterpenoid xestosaprol O (297) [307]; sponge Monanchora pulchra bisguanidine alkaloid urupodicin A (298) [308]; sponge Luffariella variabilis β-carboline alkaloid variabine B (299) [309]; and cyanobacterium Leptolyngbya sp. yoshinone A (300) [310].
| Compound/Organism * | Chemistry | Pharmacological Activity ¹ | IC₅₀ b | MMOA c | Country d | References |
|---------------------|-----------|----------------------------|--------|--------|-----------|------------|
| AdE-1 (219)/sea anemone | Peptide g | Cardiomyocyte action potential modulation | 2 nM * | Na⁺ and K⁺ current increase | ISR [236] |
| aaptamine (220)/sponge | Alkaloid g | ROS inhibition | 10 µM * | Cytokine inhibition | S. KOR [237] |
| amphirionin-4 (221)/dinoflagellate | Polyketide e | Bone marrow stromal cells proliferation stimulation | <0.1 ng/mL | Cytoskeleton protein synthesis | JPN [238] |
| astaxanthin (145)/alga | Terpenoid f | Leydig cell steroidogenesis protection | 10 µg/mL * | ROS scavenging | TWN [239] |
| bastardins 6 and 16 (222, 223)/sponge | Alkaloid g | Adipocyte differentiation inhibition | 50 µg/mL * | Adipogenesis inhibition | S. KOR [241] |
| 6,6-bieckol (224)/alga | Polyketide e | Increase G₁ cell cycle phase | 2 µM * | GAPDH and hENO1 binding | BRA, USA [242] |
| (-)-chlorizidine A (225)/bacterium | Alkaloid g | Increase G₁ cell cycle phase | 2 µM * | GAPDH and hENO1 binding | BRA, USA [242] |
| dhydroaustrasulfone alcohol (226)/soft coral | Polyketide e | PDGF-induced HASMC proliferation and angiogenesis inhibition | 10 µM * | DNA synthesis and VEGF signaling inhibition | TPN [243,244] |
| DPHC (227)/alga | Terpenoid f | UVB radiation-induced DNA damage protection | 20 µM * | Nucleotide excision repair system induction | S. KOR [245] |
| echinochrome A (204)/sea urchin | Alkaloid g | Cardiac contractility inhibition | 3 µM * | SERCA2A inhibition | BEL, S. KOR, RUS [246] |
| echinochrome A (204)/sea urchin | Alkaloid g | Increased mitochondria biogenesis and function | 5 µM * | Mitochondrial biogenesis genes upregulation | S. KOR, RUS [247] |
| eckol (228)/alga | Polyketide e | ROS suppression in cells | 10 µM * | Increased HO-1 expression | S. KOR [248] |
| eminodile SB (229)/fungus | Terpenoid f | Nonselective CB₁/CB₂ antagonist | 2.2–7.0 µM ** | Undetermined | CHE, DEU [249] |
| farnesylquinone (230)/bacterium | Polyketide e | Decreased lipid accumulation | 1 µM * | Increased PPARα activity | CHN, DEU [250] |
| FGFC1 (231)/fungus | Alkaloid g | Thrombolysis induction in vivo | 5 mg/kg * | Fibrin hydrolysis induction in vitro | CHN [251] |
| formosusin A (232)/fungus | Alkaloid g | Mammalian DNA polymerase β inhibition | 35.6 µM | Competitive and non-competitive inhibition | JPN [252] |
| fucodiphlorethol (233)/alga | Polyketide e | ROS inhibition | 10 µM * | Decreased mitochondrial loss, and caspase-9 expression | S. KOR [253] |
| gallic acid (234)/alga | Shikimate h | NO-dependent vasorelaxant effect | 12.5 µg/mL | Phospho-eNOS increase | S. KOR [254] |
| gallinamide A (235)/bacterium | Peptide f | Human cathepsin L inhibition | 5 nM | Covalent inhibition | USA [255] |
| giroline (236)/sponge | Alkaloid g | TLR 5 inhibition | 2 µg/mL | IL-8 and IL-6 inhibition | CAN, NLD, USA [256] |
| gracilins A, H, L (237–239)/sponge | Terpenoid f | mPTP opening inhibition | 1 µM * | Binding to CypD | EGY, ESP, GBR [257] |
| H. crispa polypeptides (240, 241)/sea anemone | Peptide f | Macrophage TNF-α, IL-6, and proIL-1β inhibition | | Trypsin and α-chemotrypsin inhibition | RUS, TWN [258] |
| Hyrtios sp. sesterterpene (242)/sponge | Terpenoid f | TDP-43 inhibition | 0.4 nM | TDP-43 to DNA binding inhibition | ITA, PYF [259] |
Table 3. Cont.

| Compound/Organism a | Chemistry | Pharmacological Activity i | IC<sub>50</sub> b | MOOA c | Country d | References |
|---------------------|-----------|-----------------------------|------------------|--------|-----------|------------|
| irciniaastatin A (243)/sponge | Polyketide e | TNF-α receptor 1 ectodomain shedding | 10 nM * | ERK activation induced | JPN | [260] |
| iejimalide C (244)/ascidian | Polyketide e | V-ATPase inhibitor | 0.12 μM | Bafilomycin site binding | JPN | [261] |
| Laurencia sp. indole (245)/algae | Alkaloid g | Aryl hydrocarbon receptor agonist | 10 μM * | DNA binding stimulation and CYP1A1 induction | JPN, USA | [262] |
| neopetroside A (246)/sponge | Alkaloid g | Cardiomyocyte mitochondrial upregulation | 10 μM * | Increased ATP levels and O<sub>2</sub> consumption | RUS, S. KOR | [263] |
| Phlorofucofuroeckol-A (10)/algae | Polypeptide d | Lipid accumulation inhibition | 18 μM | Decreased PPARγ expression | S. KOR | [264] |
| polytheonamide B (247)/sponge | Peptide g | One-ion pore channel permeation determined | NA | Two ion binding sites defined, but second ion excluded | JPN | [265] |
| siphonaxanthin (248)/algae | Terpenoid f | Adipogenesis inhibition | 5 μM | Transcription factor inhibition | JPN | [266] |
| spiromastixones J and L (57, 249)/fungus | Peptide g | P450 3a activity and expression regulation | 14 mg/kg *** | Active site binding determined by docking studies | CAN, CHN | [269] |
| thalassospiramide C (250)/bacterium xyloketel B (251)/fungus | Peptide g | HCAN1 inhibition | 3.4 nM | Binding to Cys115 residue | CHN, USA | [268] |
| xyloketel B (251)/fungus | Peptide g | Atherosclerotic plaque attenuation | 14 mg/kg *** | Increased eNOS activity | CAN, CHN | [269] |
| X. testudinaria lipid (252)/sponge acuminolide A (253)/dinoflagellate albatatin Ac (254)/bacterium alternariol derivatives (255–257)/sponge | Polyketide e | Pancreatic lipase inhibition | 3.11 μM | Triglyceride level decrease in vivo | CHN, ITA | [271] |
| apilamide D (258)/ascidian | Alkaloid g | Pepsin inhibition | 11 nM | Undetermined | JPN | [273] |
| australides 4 and 9 (259, 260)/fungus axinelline A (261)/bacterium brevisulcatic acid (4′,5′-dehydrodiodictyonema (262)/dinoflagellate 4′,5′-dehydrodiodictyonema (263)/algae D. metachromia sesquiterpenes (264–266)/sponge didemnaketal D and E (267, 268)/ascidian | Polyketide e | Activation of sodium channels | 20 ng/mL | Undetermined | JPN, NZL | [277] |
| | Peptide f | HCV protease inhibition | 12–52 μg/mL | Undetermined | EGY, SAU | [136] |
| | Peptide f | Na<sup>+</sup>/K<sup>+</sup>-ATPase inhibition | 3.2 μM | Undetermined | S. KOR | [274] |
| | Terpenoid f | Endo-1,3-β-D-glucanase inhibition | 0.01 μM | Undetermined | RUS | [275] |
| | Alkaloid g | COX-2 inhibition | 2.8 μM | Undetermined | CHN | [276] |
| | Polyketide e | Activation of sodium channels | 20 ng/mL | Undetermined | JPN, NZL | [277] |
| | Terpenoid f | PTP1B inhibition | 2.3 μM | Undetermined | CHN | [278] |
| | Terpenoid f | Multiple kinases inhibition | 0.97–4.8 μM | Undetermined | CHN, NLD, DEU | [279] |
| | Terpenoid f | Multiple kinases inhibition | 10 μg/mL * | Undetermined | EGY | [280] |
| Compound/Organism | Chemistry | Pharmacological Activity | IC\textsubscript{50} b | MMOA c | Country d | References |
|------------------|-----------|--------------------------|-----------------|---------|-----------|------------|
| dysiquinol D (269)/sponge Terpenoid | NF-κB inhibition | 0.81 µM | Undetermined | AUS, CHN | [281] |
| fucoxanthin (134)/alga Terpenoid | Hydroxyl radical-scavenging | 10 µg/mL | Undetermined | CHN | [282] |
| halenaquinol sulfate (270)/sponge Polyketide | CDK9 and DYRK1A inhibition | 0.5–0.61 µM | Undetermined | FRA, NZL | [283] |
| 1-hydroxyethylhalenaquinone (271)/sponge Polyketide | Proteasome-chymotrypsin-like activity inhibition | 0.19 µM | Undetermined | IDN, JPN, NLD | [284] |
| hymenialdisine derivatives (272–274)/sponge Alkaloid | Pf/GSK-3 inhibition | 0.07–0.2 µM | Undetermined | DEU, EGY, FRA, NLD | [285] |
| hymenialdisine (275)/sponge Terpenoid | CK1, CDK5, GSK3β inhibition | 0.03–0.16 µM | Undetermined | AUS | [286] |
| hyattellactone A (276)/sponge Polyketide | PTP1B inhibition | 7.45 µM | Undetermined | IDN, JPN | [287] |
| H. lactae sesterterpenoid (277)/sponge Polyketide | PTP1B inhibition | 5.2 µM | Undetermined | CHN | [288] |
| ianthelliformisamines A–C (278, 7, 8)/sponge Alkaloid | Carbonic anhydrase inhibition | 0.2–0.85 µM | Undetermined | AUS, ITA | [289] |
| incisterols A5 and A6 (279, 280)/sponge Terpenoid | PXR agonists | 10 µM * | Undetermined | ITA | [290] |
| L. crassum cembranoid (281)/soft coral Terpenoid | PPAR transcription activation | 2.07 µM | Undetermined | VNM | [291] |
| L. okamurae terpenoid (282)/alga Terpenoid | PTP1B inhibition | 4.9 µg/mL | Undetermined | CHN | [292] |
| malonganenone L (283)/sea whip Terpenoid | Lipid-lowering effect | 8.5 µM | Undetermined | CHN | [293] |
| punctaporonin K (284)/fungus Alkaloid | PDE4D inhibition | 10 µM * | Undetermined | CHN, DEU | [294] |
| psychrophilin G (285)/fungus Terpenoid | Lipid-lowering effect | 10 µM * | Undetermined | CHN | [295] |
| racemosin (286)/alga Alkaloid | PTP1B inhibition | 5.9 µM | Undetermined | CHN | [296] |
| sarcobendrin B (287)/soft coral Polyketide | PDE4 inhibition | 3.7 µM | Undetermined | CHN | [297] |
| sarsonolide A (288)/soft coral Terpenoid | PTP1B inhibition | 6.8 µM | Undetermined | CHN, HUN | [298] |
| Stachybotry sp. xanthone (289)/fungus Polyketide | COX-2 inhibition | 8.9 µM | Undetermined | CHN | [299] |
| S. thunbergii alkapolynene (290)/alga Polyketide | Soybean LOX inhibition | 5 µM | Undetermined | JPN, S. KOR | [300] |
| shinorine (291)/alga Alkaloid | C. histolyticum collagenase inhibition | 104 µM | Undetermined | AUT | [301] |
| Compound/Organism | Chemistry | Pharmacological Activity | IC$_{50}$ | MMOA | Country | References |
|--------------------|-----------|--------------------------|-----------|------|---------|------------|
| sinularone D (292)/soft coral | Polyketide $^e$ | NF-κB inhibition | 10 µg/mL $^*$ | Undetermined | CHN | [302] |
| N-(2-benzenepropanoic acid) stachybotrylactam (293)/fungus stronglylporhinore-13-14 (294)/sponge | Alkaloid $^g$ | Triglyceride and cholesterol inhibition | 10 µM $^*$ | Undetermined | CHN, DEU | [303] |
| swinhoeisterol A (295)/sponge | Terpenoid $^i$ | Hu proteasome 20S inhibition | 2.1 µM | Undetermined | JPN | [304] |
| thunberol (296)/alga | Terpenoid $^i$ | (h)P300 acetyltransferase inhibition | 2.7 µM | Undetermined | ITA, CHN, USA | [305] |
| xestosaprol O (297)/sponge | Terpenoid $^i$ | Proteasome-chymotrypsin-like activity inhibition | 2.24 µg/mL | Undetermined | CHN | [306] |
| urupocidin A (298)/sponge | Alkaloid $^g$ | iNOS expression induction | 10 µM $^*$ | Undetermined | RUS, TWN | [307] |
| variabine B (299)/sponge | Alkaloid $^g$ | Proteasome-chymotrypsin-like activity inhibition | 4 µg/mL | Undetermined | IDN, JPN, NLD | [308] |
| yoshinone A (300)/cyanobacterium | Polyketide $^e$ | Triglyceride inhibition | 0.4 µM | Undetermined | JPN | [309] |

$^*$ Organism, Kingdom Animalia: ascidian (Phylum Chordata), soft corals, sea whips, and sea anemone (Phylum Cnidaria), dinoflagellates (Phylum Dinoflagellata), sea urchin (Phylum Echinodermata), sponge (Phylum Porifera); Kingdom Fungi: fungus; Kingdom Plantae: alga; Kingdom Monera: bacterium; $^b$ IC$_{50}$: concentration of a compound required for 50% inhibition in vitro; $^*$: estimated IC$_{50}$; $^{**}$: Ki; $^{***}$ in vivo study; $^c$ MMOA: molecular mechanism of action; $^d$ Country: AUS: Australia; AUT: Austria; BEL: Belgium; BRA: Brazil; CAN: Canada; CHE: Switzerland; CHN: China; DEU: Germany; EGY: Egypt; FRA: France; ESP: Spain; GBR: United Kingdom; HUN: Hungary; IDN: Indonesia; ISR: Israel; ITA: Italy; JPN: Japan; NLD: The Netherlands; NZL: New Zealand; PYF: French Polynesia; RUS: Russian Federation; SAU: Saudi Arabia; S. KOR: South Korea; TWN: Taiwan; VNM: Vietnam; $^e$ Chemistry: Polyketide; $^i$ Terpene; $^g$ Nitrogen-containing compound; $^h$ shikimate; $^{Abbreviations}$: ACAT: acyl-CoA:cholesterol acyl-transferase; CB: cannabinoid; CDK: cyclin-dependent kinase; COX-2: cyclooxygenase 2; CK1: casein kinase 1; CypD: cyclophilin D; DDYRK: dual-specificity, tyrosine phosphorylation regulated kinase; DPHC: diphlorethohydroxycarmalol; eNOS: endothelial nitric oxide synthase; ERK: extracellular signal-regulated kinase; GAPDH: D-glyceraldehyde-3-phosphate dehydrogenase; GSK3$^\beta$: glycogen synthase kinase 3; HASMC: human aortic smooth muscle cells; HCAN1: human calpain 1 protease; HCV: hepatitis C virus; HEN01: human alpha-enolase; hu: human; HO-1: hemeoxygenase-1; IDO1: indoleamine 2, 3 dioxygenase; IL: interleukin; iNOS: inducible nitric oxide synthase; LOX: lipooxygenase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; mPTP: mitochondrial permeability transition pore; PDGF: platelet-derived growth factor; PDE4: phosphodiesterase 4; PPAR: peroxisome proliferator-activated receptor; PTP1B: protein tyrosine phosphatase 1B; PXR: pregnane-X-receptor; ROS: reactive oxygen species; SERCA2A: SR Ca$^{2+}$ ATPase 2A; TLR5: Toll-like receptor 5; TDP-43: trans-activation response DNA-binding protein of 43 kDa; UVB: ultraviolet B; V-ATPase: vacuolar-type H$^+$-ATPase; VEGF: vascular endothelial growth factor.
Figure 3. Cont.
Figure 3. Cont.
Figure 3. Cont.
Figure 3. Cont.

polytheonamide B (247)

siphonaxanthin (248)

spiromastixone L (249)
Figure 3. Cont.

thalassospiramide C (250)

xyloketal B (251)

X. testudinarina lipid 252

acuminolide A (253)

ahpatinin Ac (254)

apliamide D (258)

alternariol derivatives
255 R=SO3H, R'=Me
256 R=H, R'=Me
257 R=R'=H

austalide 4 (259)
austalide 9 (260)
axinelline A (261)

Figure 3. Cont.
brevisulcatic acid-4 (262)

4',5'-dehydrodiodictyonema A (263)

D. metachromia sesquiterpenes

264

265

266

didemnaketal D (267) \( R = \text{CO}_2\text{Me}, R' = \text{OAc} \)
didemnaketal E (268) \( R = \text{CO}_2\text{Et}, R' = \text{OH} \)
dysiquinol D (269)

halenaquinol sulfate (270)

1-hydroxyethylhalenaquinone (271)

Figure 3. Cont.
hymenialdisine (275)

\[
\begin{align*}
&\text{Hymenialdisine derivatives} \\
\text{272} & \quad R' = R'' = H \\
\text{273} & \quad R' = \text{Br}, \ R'' = \text{H} \\
\text{274} & \quad R' = R'' = \text{Br}
\end{align*}
\]

H. lachne sesterterpenoid 277

Ianthelliformisamine A (278)

Incisterol A5 (279)

Incisterol A6 (280)

L. crassum cembranoid 281

L. okamurai terpenoid 282

Malonganenone L (283)

Figure 3. Cont.
psychrophilin G (285)
punctaporonin K (284)
S. thunbergii alkapolyene 290

racemosin C (286)

sarsolilide A (288)
Stachybotry sp. xanthone 289

shinorine (291)
sinarone D (292)

N-(2-benzenepropanoic acid) stachybotrylactam (293)

strongylophorine-13/-14 (294)

swinhoeisterol A (295)
thunberol (296)

Figure 3. Cont.
5. Reviews on Marine Pharmacology and Pharmaceuticals

In 2014–2015, several reviews covered general and/or specific areas of marine preclinical pharmacology: (a) Marine pharmacology and marine pharmaceuticals: new marine natural products and relevant biological activities published in 2014 and 2015 [311,312]; marine peptides, bioactivities and applications [313]; bioactive terpenes from marine-derived fungi [314]; bioactive marine natural products from actinobacteria with unique chemical structures [315]; Baltic cyanobacteria as a source of biologically active compounds [316]; biological targets of marine cyanobacteria natural products [317]; marine mussels as a source for bioactive compounds for human health [318]; pharmacological potential of cephalopod ink in drug discovery [319]; pharmacologically active Brazilian octocorals [320]; bioactive natural products isolated from marine microorganisms from Brazil [321]; statistical analysis of marine natural product bioactivity from 1985–2012 [322]; metagenomics and marine natural products drug discovery [323]; new horizons for selected marine natural products as drug leads [324]; marine-sourced agents in clinical and late preclinical development [325]; the global marine pharmaceutical pipeline in 2019: approved compounds and those in Phase I, II, and III of clinical development https://www.midwestern.edu/departments/marinepharmacology.xml. (b) Antimicrobial marine pharmacology: biophysical properties of anti-lipopolysaccharide antimicrobial peptides isolated from marine fish [326]; marine peptides and their anti-microbial activities [327]; marine membrane-active peptides as antimicrobials [328]; marine fungi antibacterial compounds [329]. (c) Antiviral marine pharmacology: marine natural products with antiviral potential [330]; antiviral activity in marine fungi-derived natural products [331]. (d) Antiprotozoal and antimalarial marine pharmacology: antiprotozoal activity in marine natural products isolated from marine algae [332]; marine indole alkaloids as potential leads for antiprotozoal drugs [333]; antimalarial potency of the manzamine β-carboline alkaloids [334]. (e) Immuno- and anti-inflammatory marine pharmacology: marine diterpenoids as potential anti-inflammatory agents [335]; microalgal bioactive compounds for inflammation and cancer [336]. (f) Cardiovascular and anti-diabetic marine pharmacology: marine-derived natural products as a source of cardiovascular protective agents [337]; antioxidant phlorotannins derived from marine algae [338]; antioxidant carotenoids isolated from marine Gram-positive bacteria [339]; brown alga-derived fucoxanthin for diabetes therapy [340]; bioactive compounds from seaweed for diabetes [341]. (g) Nervous system marine pharmacology: astaxanthin as a potential neuroprotective agent [342]; origin, distribution, toxicity, and therapeutic uses of the marine neurotoxin tetrodotoxin [343]; marine natural products with neuroprotective activity [344];

Figure 3. Marine pharmacology in 2014–2015: marine compounds with miscellaneous mechanisms of action.
marine-terpenoid gracilins as promising compounds for Alzheimer’s disease [345]; new marine drugs for Alzheimer’s disease treatment [346]. (h) Miscellaneous molecular targets and uses: matrix metalloproteinase inhibitors isolated from edible marine algae [347]; marine natural products that targeting apoptosis signaling pathways [348]; scytonemin and emerging biomedical applications [349]; antiobesity effects of the carotenoid fucoxanthin [350]; therapeutic potential of astaxanthin [351]; pharmacological properties of marine coumarins [352].

6. Conclusions

The current marine pharmacology 2014–2015 review is a sequel to the marine preclinical pharmacology pipeline review series initiated in 1998 [1–9], and consolidates the peer-reviewed preclinical marine pharmacological literature published during 2014–2015. The global preclinical marine pharmacology research involved chemists and pharmacologists from 43 countries, namely, Australia, Austria, Bangladesh, Belgium, Brazil, Canada, China, Colombia, Costa Rica, Cuba, Denmark, Egypt, Finland, France, French Polynesia, Germany, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Papua New Guinea, Portugal, Russian Federation, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sri Lanka, Switzerland, Taiwan, Thailand, United Kingdom, Vietnam, and the United States. Thus, during 2014–2015, the marine preclinical pharmaceutical pipeline continued to provide novel pharmacology that provided novel leads for the marine clinical pharmaceutical pipeline. As shown at the global marine pharmaceutical pipeline website, https://www.midwestern.edu/departments/marinepharmacology.xml, there are currently 9 approved marine-derived pharmaceuticals, and an additional 31 compounds are either in Phase I, II, and III of clinical pharmaceutical development.

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