Review

Natural Nitrogenous Sesquiterpenoids and Their Bioactivity: A Review

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Abstract: Nitrogenous sesquiterpenoids from natural sources are rare, so unsurprisingly neither the potentially valuable bioactivity nor the broad structural diversity of nitrogenous sesquiterpenoids has been reviewed before. This report covers the progress during the decade from 2010 to February 2020 on the isolation, identification, and bioactivity of 391 nitrogen-containing natural sesquiterpenes from terrestrial plant, marine organisms, and microorganisms. This complete and in-depth review should be helpful for discovering and developing new drugs of medicinal value related to natural nitrogenous sesquiterpenoids.

Keywords: nitrogenous sesquiterpenoids; elastraceae; marine sponge; fungi; bioactivities.

1. Introduction

The natural products commonly termed ‘secondary metabolites’ in contrast to ‘primary metabolites’, are produced by organisms in order to provide an evolutionary benefit [1]. Natural products as a major chemical resource, have played a significant role over the last 200 years in treating and preventing diseases, and continue to serve as important agents in modern drug discovery due to their characteristic chemical spatial orientation, which enables them to interact with their natural and other biological targets [1–4]. Recently, half of new drugs reported were naturally occurring or constructed on the basis of some natural chemical framework [4–6].

Sesquiterpenoids are the largest class of natural terpenoids, with a structural diversity that includes thousands of compounds and more than 100 skeletal types [7]. Many of them show ‘drug-like’ chemical properties, including alkylation center reactivity, lipophilicity, and favorable molecular geometry and electronic features, and have attracted considerable interest due to their pronounced biological activities [8,9]. Meanwhile, sesquiterpenoids that contain nitrogen bonds constitute a fascinating group with enormous structural diversity [10]. Interestingly, it is notable that nitrogenous sesquiterpenoids are rare in natural sources, and there are only a few hundred such compounds that contain the element known to be produced by certain species. Functionally and biologically important to humans, have caught the attention of a number of scientists, and extensive
phytochemical and biological investigations of nitrogenous sesquiterpenoids from natural sources have been carried out by researchers at the recent ten years [10–12].

While the scientific community is generally aware of the rarity of the N bond in natural sesquiterpenoids, and there are many reviews providing extensive coverage on sesquiterpenoids [11,12], including the naturally occurring desesquiterpenoids [1,13,14], natural products containing a nitrogen-nitrogen bond [15] or nitrogen-sulfur bond [16], neither the potentially valuable bioactivity nor the broad structural diversity of nitrogenous sesquiterpenoids has been systematically reviewed during the past ten years.

In this review, nitrogenous sesquiterpenoids from biological sources, including plants, microorganisms, and marine resources, will be considered. In order to be as comprehensive and clear as possible, the natural nitrogenous sesquiterpenoids have been segregated by structural class and compounds covered in the past decade included where appropriate. This report provides a systematic review of the isolation, structural characterization and biological activities of these compounds since 2010, if known.

2. Species Containing Nitrogenous Sesquiterpenoids and Their Bioactivities

2.1. Dihydroagarofuran Sesquiterpenoids

Nitrogen-containing dihydroagarofuran sesquiterpenoids feature several ester groups on a highly oxygenated tricyclic scaffold, and their polyesterified macroclide sesquiterpenoid pyridine alkaloids possess a characteristic macrocyclic diolactone skeleton consisting of a dicarboxylic acid moiety, 2-(carboxyalkyl)nicotinic acid, and a polyoxygenated dihydro-β-agarofuran sesquiterpenoid (Figure 1 and Table 1). The hydroxyl groups of the latter are usually esterified by various organic acids including acetic, benzoic, furanoic, nicotinic, and cinnamic acids. The 2-(carboxyalkyl)nicotinic acid moiety originates from evonic acid, wilfordic acid, hydroxywilfordic acid, or their congeners. The number, position, and configuration of these substituents create a large novel chemical diversity and exhibit a broad range of biological activities.

Dihydroagarofuran sesquiterpenoids were considered the most widespread and characteristic metabolites of the plants of the Celastraceae. Compounds 1–12 were isolated from the roots of *Maytenus mekongensis* [17]. Compounds 1–5 having wilfordic acid moieties, either with or without a 9′-OAc group, exhibited comparable antiplasmodial activities, with IC₅₀ values of 3.1×10⁻³, 3.9×10⁻³, 3.5×10⁻³, 3.1×10⁻³, and 2.5×10⁻³ mM respectively, while compounds 10–12 with evonic acid moieties showed no inhibitory activity. Compounds 12–29 were extracted from the dried roots of *Tripterygium wilfordii* [18]. Compound 22 displayed 22.3% inhibitory activity against HSV2 in vitro at 0.5 mg/mL, and acyclovir 66.3% inhibitory activity at 0.5 mg/mL. Compound 28 showed 31.7% inhibitory activity at 0.25 mg/mL, while acyclovir displayed 60.6% inhibitory activity at 0.25 mg/mL. Compounds 30 and 31 were obtained from the fruits of *Celastrus orbiculatus* Thunb [19]. Hypoglaunines E (32) and F (33) have been purified from the root barks of *Tripterigium hypoglauca* and showed no cytotoxic activities against five cancer cell lines [20]. Tripersinines A–H, L (compounds 34–42), peritassine A (26), wilfordine A (43), hypoglaunine A (44), hypoglaunine E (32), wilfordine E (45), euonine (46), wilfortrine (21), euonymine (12) were extracted from the leaves of *Tripterygium wilfordii*, and compounds 26, 34, 43, and 46 showed moderate inhibitory effects on nitric oxide production in LPS-induced macrophages at 5 μM [21]. Compounds 47–49 were identified from the thents of *Euonymus alatus* [22]. Tripersinines M–T (compounds 50–57) and wilforicine (18) have been extracted from the leaves of *Tripterygium wilfordii*, and compounds 50, 51, 54, 57, and 18 showed moderate inhibitory activities on NO production and no influence on cell viability by the MTT method, the other compounds exhibited weak effects [23]. Compounds 7, 25, 58–91 were obtained from the dried roots of *Tripterygium wilfordii* [24]. Tripterygiumine Q (81) exhibited immunosuppressive activity with an IC₅₀ value of 8.67 μM, and no cytotoxicity was observed even at a dose of 100 μM. Triptonine B (82) not only exhibited immunosuppressive activity with an IC₅₀ value of 4.95 μM, but also showed cytotoxicity with an IC₅₀ value of 26.41 μM. Compounds 92–95 were isolated from the leaves of *Maytenus spinosa* [25], and the isolates displayed no anti-HIV activity. Tripterygiumines S-W (96–100),
wilfornine A (101), wilfornine D (102), tripfordine A (103), 2-debenzoyl-2-nicotinoylwilforine (104) along with 12–13, 18–20, 25, 75, and 87 were purified from the roots of the *Tripterygium wilfordii*, and found that 13 and 96 possessed potent nitric oxide inhibitory activity with IC₅₀ values ranging from 2.99 to 28.80 μM, without any effect on the cell viability of RAW 264.7 cells [26]. Accordingly, compounds 13 and 96, especially 13, were identified as promising candidates for further scientific investigation of their potential use as anti-inflammatory agents. Compound 105 was obtained from the whole plants of *Parnassia wightiana*, and showed some cytotoxic activities against NB4, MKN-45 and MCF-7 cells at 20 μM [27]. Triptregelines A-J (106–115), regeldidine (28), 1α,6β,15-triacetoxy-8α-hydroxy-D-enantiomer (30), 1-O-Benzoyl-1-deacetyl-4-deoxyaltamine (121) and 1,2-O-dibenzyloxy-1,2-deacetyl-4-deoxyaltamine (122) exhibited strong larvicidal activity on the A. aegypti Paea strain with LD₅₀ values of 9.4 (95% CI: 6.5–10.0) and 2.7 μM (95% CI: 1.9–2.9), respectively. Triptersinine U (124), hypoglaunine B (125) together with 26, 32, 33, 43, 44, and 46 were isolated from the roots of *Tripterygium wilfordii*, but all dihydroagarofuran derivatives didn’t show cytotoxicity against six human tumor cell lines (HepG2, Hep3B, Bcap37, U251, MCF-7 and A549) [31]. Neuroprotective triptersinine Z₄–Z₁₂ (126–130, 132–137) and euojaponine C (131) have been obtained from the leaves of *Tripterygium wilfordii* [32,33], and 126, 127, 129–131 increased cell viability of the okadaic acid-treated PC12 cells from 60.4 ± 23.0% to 72.4 ± 14.1, 71.5 ± 11.5, 75.7 ± 15.6, 81.2 ± 13.1, and 86.2 ± 25.5% at 10 μM, respectively [32]. At 10 μmol/L, compounds 132 and 133 showed moderate inhibitory effects on NO production in LPS-induced macrophages with inhibitory rate at 31.2 ± 3.6 and 40.9 ± 4.3 [33]. Two new sesquiterpene pyridine alkaloids, Chinese bittersweet alkaloid A (138) and Chinese bittersweet alkaloid B (139) were isolated from the rootbarks of *Celastrus angulatus* [34]. Monimins I (140) and II (141) have been extracted from the leaves of *Monimopetalum chinense* [35]. Tripfordine C (142) and tripteryford E (143) have been obtained from the leaves of *Tripterygium wilfordii*, and 142 exhibited the better protective activity against human neuroblastoma SH-SY5Y cell injury induced by H₂O₂ with 76.63% cell viability comparing with the positive control Trolox (69.84%) at 12.5 μM [36]. Celaspaculin G (144) was purified from the seeds of *Celastruspaniculatus*, and with non lifespan-extending effect on the nematode *Caenorhabditis elegans* [37].
Figure 1. Twelve types (A–L) of dihydroagarofuran sesquiterpenoid skeletons.
Table 1. Reported structures of dihydroagarofuran sesquiterpenoids 1–144.

| No | Name                              | R₁  | R₂  | R₃  | R₄  | R₅  | R₆  | R₇  | R₈  | Type | Ref     |
|----|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|------|---------|
| 1  | Mekongensine                      | OAc | OBz | βOAc | βOAc | OAc | OH  | βOAc | OAc | H    | A       | [17]    |
| 2  | 7-epi-Mekongensine                | OAc | OBz | αOAc | βOAc | OAc | OH  | βOAc | OAc | H    | A       | [17]    |
| 3  | 1-O-Benzoyl-1-deacetylmekongensine| OBz | OBz | βOAc | βOAc | OAc | OH  | βOAc | OAc | H    | A       | [17]    |
| 4  | 9′-Deacetoxymekongensine 1-O-Benzoyl-1-deacetoxymekongensine | OBz | OBz | βOAc | βOAc | OAc | OH  | βOAc | OAc | H    | A       | [17]    |
| 5  | 7-epi-Euopajonine A               | OBz | OH  | αOAc | βOAc | OAc | OH  | βOAc | OAc | H    | CH₅     | B       | [17]    |
| 6  | 2-O-Benzoyl-2-deacetylmayteine    | OBz | OAc | βOAc | βOAc | OAc | OH  | βOBz | OAc | CH₅   | B       | [17,24] |
| 7  | 7-epi-5-O-Benzoyl-5-deacetylperitassine A | OAc | OBz | αOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | C       | [17]    |
| 8  | 7-epi-Euonymine                   | OAc | OAc | αOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [17]    |
| 9  | Mayteine                          | OBz | OAc | βOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [17]    |
| 10 | 7-epi-Mayteine                    | OBz | OAc | αOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [17]    |
| 11 | Euonymine                         | OAc | OAc | βOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [17]    |
| 12 | 9′-O-Acetyl-7-deacetoxy-7-oxowilfortine | OAc | OAc | O   | βOAc | OAc | OH  | βOFu | OAc | H    | A       | [18,26] |
| 13 | 9′-O-Acetylwilfortine             | OAc | OAc | βOAc | βOAc | OAc | OH  | βOFu | OAc | H    | A       | [18]    |
| 14 | 9′-O-Furanoylwilfortine           | OAc | OAc | βOAc | βOAc | OAc | OH  | βOFu | OAc | H    | A       | [18]    |
| 15 | 7-O-Benzoyl-5,7-dideacetylwilfortine | OAc | OAc | βOAc | βOAc | OAc | OH  | βOBz | OAc | H    | A       | [18]    |
| 16 | Wilfortine                        | OAc | OAc | βOAc | βOAc | OAc | OH  | βOFu | OAc | H    | A       | [18,21,26] |
| 17 | Wilfargin                         | OAc | OAc | βOAc | βOAc | OAc | OH  | βOFu | OAc | H    | A       | [18,21,26] |
| 18 | Wilfordine                        | OAc | OAc | βOAc | βOAc | OAc | OH  | βOFu | OAc | H    | A       | [18,23,26] |
| 19 | Wilfortine                        | OAc | OAc | βOAc | βOAc | OAc | OH  | βOBz | OAc | H    | A       | [18,26] |
| 20 | Wilfortine                        | OAc | OAc | βOAc | βOAc | OAc | OH  | βOBz | OAc | H    | A       | [18,26] |
| 21 | Wilformine                        | OAc | OAc | βOAc | βOAc | OAc | OH  | βOAc | OAc | H    | A       | [18]    |
| 22 | Wilforidine                       | OAc | OAc | βOAc | βOAc | OAc | OH  | βOAc | OAc | H    | A       | [18]    |
| 23 | Cangorinine E-1                   | OAc | OBz | βOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [18]    |
| 24 | Ebenofoline E-II                  | OBz | OBz | βOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [18]    |
| 25 | Neeuonymine                       | OAc | OH  | βOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | B       | [18,24,26] |
| 26 | Peritassine A                     | OAc | OAc | βOAc | βOAc | OAc | OH  | βOAc | OAc | CH₅   | C       | [18,21,31] |
| 27 | Wilfortine G                      | OAc | OAc | βONic | βOAc | OAc | OH  | βOAc | OAc | CH₅   | C       | [18]    |
| 28 | Regelidine                        | OBz | ONic | H    | αOBz | H   | OH  | H    | H    | D    | [18,24,28] |
| 29 | 9-O-trans-Cinnamoyl-9-debenzoylregelidine | OBz | ONic | H    | αO/Cin | H | OH  | H    | H    | D    | [18]    |
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|--------------------------|----------|
| 1β-Acetoxy-8α,9β-dibenzoyloxy- | 1β,2β-Diacetoxy-9α-benzoyloxy- |
| 13-nicotinoyloxy-β- | 13-nicotinoyloxy-β- |
| dihydroagarofuran | dihydroagarofuran |
| 30 | 31 |
| OAc | OAc | H | H | αOBz | βOBz | ONic | H | H | H | H | H | D | [19] |
| 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
| Hypoglaunine E | Hypoglaunine F | Triptersinine A | Triptersinine B | Triptersinine C | Triptersinine D | Triptersinine E | Triptersinine F | Triptersinine G | Triptersinine H | Triptersinine L | Wilfordinine A | Hypoglaunine A | Wilfordinine E | Eunovine | Eunovine | Neoevovine | 1β,2β,5α,8β,11-Pentaacetoxy-4α-hydroxy-3α-(2-methylbutanoyl)-15-nicotinoyl-7-oxo-dihydroagarofuran | Triptersinine M | Triptersinine N | Triptersinine O | Triptersinine P | Triptersinine Q | Triptersinine R | Triptersinine S | Triptersinine T | Tripterygiumine A | Tripterygiumine B | Tripterygiumine C | |
| OAc | OAc | OH | βOAc | βOAc | βOAc | OAc | OH | OH | βOAc | OH | CH₃ | C | [20,21,31] | OAc | OAc | βOAc | βOAc | βOAc | OAc | OH | OH | βOAc | OH | CH₃ | C | [20,21,31] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | CH₃ | G | [22] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | CH₃ | G | [22] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] | OAc | OAc | OAc | OAc | OAc | OAc | OH | αOAc | OAc | OH | αOAc | H | H | D | [23] |
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|---|---|
| 61 | Tripterygiumine D | OH | OBz | βOH | βOH | OH | OH | βOH | H | CH₃ | B | [24] |
| 62 | Tripterygiumine E | OAc | OH | βOAc | βOAc | OAc | OH | βOFu | H | CH₃ | B | [24] |
| 63 | Tripterygiumine F | OAc | OFu | βOAc | βOAc | OAc | OH | βOBz | H | CH₃ | B | [24] |
| 64 | Tripterygiumine G | OAc | OBz | βOAc | βOAc | OAc | OH | βOFu | H | CH₃ | B | [24] |
| 65 | Tripterygiumine H | OH | OAc | βOH | βOH | OH | OH | βOH | H | CH₃ | B | [24] |
| 66 | Tripterygiumine I | OAc | OH | βOAc | βOAc | OAc | OH | βOBz | H | CH₃ | B | [24] |
| 67 | Tripterygiumine J | OAc | OH | βOH | βOAc | OAc | OH | βOAc | H | CH₃ | B | [24] |
| 68 | Tripterygiumine K | OAc | OH | βOAc | βOAc | OAc | OBz | OH | βOH | H | CH₃ | B | [24] |
| 69 | Tripterygiumine L | OAc | OH | βOAc | βOAc | OAc | OH | βOAc | H | CH₃ | B | [24] |
| 70 | Hyponine D | OAc | OBz | βOAc | βOAc | OAc | OH | βONic | H | CH₃ | B | [24] |
| 71 | Hexadesacetylhexamonymine | OH | OH | βOH | βOH | OH | OH | βOH | H | CH₃ | B | [24] |
| 72 | Euojaponine A | OAc | OBz | OH | βOAc | βOAc | OAc | OH | βOAc | H | CH₃ | B | [24] |
| 73 | Hyponine C | OAc | OAc | βOAc | βOAc | OBz | OH | βOAc | H | CH₃ | B | [24] |
| 74 | 7-Acetyloxy-1α,5α,11β-diacetyl-7-deoxyevonine | OAc | OAc | βOAc | βOAc | OBz | OH | βOH | H | CH₃ | B | [24] |
| 75 | 4-Hydroxy-7-epi-chuchuhuanine E-V | OAc | OAc | βOAc | βOAc | OAc | OH | βOH | H | CH₃ | B | [24,26] |
| 76 | Wilforidine F | OAc | OBz | βOAc | βOAc | OAc | OH | βOH | H | CH₃ | B | [24] |
| 77 | Tripterygiumine M | OAc | OH | O | βOAc | βOAc | OAc | OH | βOBz | H | H | A | [24] |
| 78 | Tripterygiumine N | OAc | OH | O | βOAc | βOAc | OAc | OH | βOBz | OFu | H | A | [24] |
| 79 | Tripterygiumine O | OAc | OH | βOAc | βOAc | OAc | OH | βOFu | OBz | H | A | [24] |
| 80 | Tripterygiumine P | OH | OAc | βOH | βOH | OH | OH | βOH | OBz | H | A | [24] |
| 81 | Tripterygiumine Q | OH | OAc | βOH | βOH | OH | OH | βOH | OFu | H | A | [24] |
| 82 | Triptonine B | OAc | OAc | βOAc | βOAc | OAc | OH | βOFu | OFu | H | A | [24] |
| 83 | 1-Desacylwilforidine | OH | OAc | βOAc | βOAc | OAc | OH | βOFu | H | H | A | [24] |
| 84 | Alatamine | OAc | OAc | O | βOAc | βOAc | OAc | OH | βOBz | OH | H | A | [24] |
| 85 | Alatusine | OAc | OAc | βOAc | βOAc | OAc | OH | βOAc | OH | H | A | [24] |
| 86 | Wilforzine | OAc | OH | βOAc | βOAc | OAc | OH | βOAc | OH | H | A | [24] |
| 87 | Wilforjine | OAc | OAc | βOAc | βOAc | OAc | OH | βOH | H | H | A | [24,26] |
| 88 | Tripterygiumine R | ONic | OH | H | αObz | H | OH | H | H | H | D | [24] |
| 89 | 1β,5α,11-Triacetoxy-7β-benzoyle-4α-hydroxy-8β- nicotinoyl-dihydroagarofuran | OAc | OAc | βOBz | αONic | OAc | OH | H | H | H | D | [24] |
| 90 | Wilforcidine | OBz | ONic | H | αOTCin | H | OH | H | H | H | D | [24] |
| 91 | 5α-Benzoyle-4α-hydroxy-1β,8α- dinicotinoyl-dihydroagarofuran | ONic | OBz | H | αONic | H | OH | H | H | H | D | [24] |
| 92 | 1α,2α,6β,8β,9α,15-Hexacetotxy-4β-hydroxy-3β,13-[2′-3-
| No. | Name                                      | OAc | OH  | O   | βOAc | OAc | OH  | αOAc | H   | H   | J   | Ref. |
|-----|------------------------------------------|-----|-----|-----|------|-----|-----|------|-----|-----|-----|------|
| 93  | (3-carboxybutyl)nicotinic acid-dicarbolactone-β-dihydroagarofuran |     |     |     |      |     |     |      |     |     |     | [25] |
| 94  | (3-carboxybutyl)nicotinic acid-dicarbolactone-β-dihydroagarofuran |     |     |     |      |     |     |      |     |     |     | [25] |
| 95  | Tripterygiumine S                        | OAc | OAc | O   | βOAc | OAc | OH  | βOH  | OFu | H   | A   | [26] |
| 96  | Tripterygiumine T                        | OAc | OH  | O   | βOAc | OAc | OH  | βOH  | OH  | H   | A   | [26] |
| 97  | Tripterygiumine U                        | OAc | OAc | βOAc| βOAc | OAc | OH  | βOH  | H   | H   | A   | [26] |
| 98  | Tripterygiumine V                        | OAc | OAc | βOAc| βOAc | OAc | OH  | βOH  | OBz | H   | A   | [26] |
| 100 | Tripterygiumine W                        | OAc | OAc | O   | βOAc | OAc | OH  | βOH  | H   | CH₃ | B   | [26] |
| 101 | Wilforine A                              | OAc | OAc | O   | βOAc | OAc | OH  | βOH  | OBFz| H   | A   | [26] |
| 102 | Wilforine D                              | OAc | OAc | βOAc| βOAc | OAc | OH  | βOH  | OFu | H   | A   | [26] |
| 103 | Tripfordine A                            | OAc | OAc | βOAc| βOAc | OAc | OH  | βOH  | OH  | H   | A   | [26] |
| 104 | 2-Debenzoyl-2-nicotinoyl wilforine (+)-(1R,2S,4S,5S,6R,7R,9S,10R)-1,2,15-Triacetoxy-9-benzyloxy-6-nicotinoyl oxydihydro-β-agarofuran | OAc | OAc | βOAc| βOAc | OAc | OH  | βONic| H   | H   | A   | [26] |
| 105 | Triptregeline A                          | OAc | ONic| H   | βOAc | OAc | OH  | αOAc | H   | H   | E   | [27] |
| 106 | Triptregeline B                          | ONic| OAc | αOAc| αOBz | OAc | OH  | αOAc | H   | H   | E   | [28] |
| 107 | Triptregeline C                          | ONic| OAc | αOBz| OAc  | OH  | H   | H   | H   | E   | [28] |
| 108 | Triptregeline D                          | OFu | OAc | αONic| αOBz | OAc | OH  | H   | H   | E   | [28] |
| 109 | Triptregeline E                          | OFu | OAc | αONic| αOBz | OAc | OH  | H   | H   | E   | [28] |
| 110 | Triptregeline F                          | OAc | OAc | αONic| αOBz | OAc | OH  | H   | H   | E   | [28] |
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|---|---|
| 112 | Triptregeline G |
| 113 | Triptregeline H |
| 114 | Triptregeline I |
| 115 | Triptregeline J |
| 116 | 1α, 6β, 15-Triacetoxy-8α-benzoyloxy-4β-hydroxy-19α-(3-nicotinoyloxy)-dihydro-β-agarofuran |
| 117 | Dimacroregeline A |
| 118 | Dimacroregeline B |
| 119 | Triptonine A |
| 120 | 4-Deoxyalatamine |
| 121 | 1-O-Benzoyl-1-deacetyl-4-deoxyalatamine |
| 122 | 1, 2-O-Dibenzoyl-1, 2-deacetyl-4-deoxyalatamine |
| 123 | 4-Deoxyisowilfordine |
| 124 | Triptersinine U |
| 125 | Hypoglaunine B |
| 126 | Triptersinine Z4 |
| 127 | Triptersinine Z5 |
| 128 | Triptersinine Z6 |
| 129 | Triptersinine Z7 |
| 130 | Triptersinine Z8 |
| 131 | Euojaponine C |
| 132 | Triptersinine Z9 |
| 133 | Triptersinine Z10 |
| 134 | Triptersinine Z11 |
| 135 | Triptersinine Z12 |
| 136 | Triptersinine Z13 |
| 137 | Triptersinine Z14 |
| 138 | Chinese bittersweet alkaloid A |
| 139 | Chinese bittersweet alkaloid B |
| 140 | Monimin I |
| 141 | Monimin II |
| 142 | Tripteryford C |
| 143 | Tripteryford E |
| 144 | Celaspaculin G |

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|---|---|
| 116 | OAc OAc αOBz αONic OAc OAc OH H H H E [28] |
| 117 | OH OAc H αOH - OH αOH H CH₃ K [29] |
| 118 | OH OAc OAc αOH - OH αOH H CH₃ K [29] |
| 119 | OAc OAc - αOAc - OH αOAc H CH₃ L [29] |
| 120 | OAc OAc O αOAc OAc H αOAc OH H I [30] |
| 121 | OBz OAc O αOAc OAc H αOAc OH H I [30] |
| 122 | OBz OAc O αOAc OAc H αOBz OH H I [30] |
| 123 | OAc OAc βOAc αOAc OAc H αOBz OH H J [30] |
| 124 | OAc OAc βOAc βOAc OAc OH βOAc αONic ONic D [31] |
| 125 | OAc OAc βOAc βOAc OAc OH βOAc OH CH₃ C [31] |
| 126 | OAc OAc OAc OAc H H H H D [32] |
| 127 | OAc OAc OAc OAc H H H H D [32] |
| 128 | OAc OAc OAc OAc H H H H D [32] |
| 129 | OAc OAc OAc OAc H H H H D [32] |
| 130 | OAc OAc OAc OAc H H H H D [32] |
| 131 | OBz OBz βOAc βOAc OAc OH βOH H CH₃ B [32] |
| 132 | OAc OAc OAc OAc H H H H D [33] |
| 133 | OAc OAc OAc OAc H H H H D [33] |
| 134 | OAc OAc βONic βOFu OAc OH H H H D [33] |
| 135 | OAc OAc βONic βOFu OAc OH H H H D [33] |
| 136 | OAc OAc βONic βOFu OAc OH H H H D [33] |
| 137 | OAc OAc βONic βOFu OAc OH H H H D [33] |
| 138 | OAc OAc βONic βOFu OAc OH βOH H CH₃ B [34] |
| 139 | OAc OAc βONic βOFu OAc OH βOH H CH₃ B [34] |
| 140 | OAc OAc H αOAc H H H H E [35] |
| 141 | OAc OAc αOH αOBz H H H H E [35] |
| 142 | OAc OAc βOAc αOAc OAc H αOAc βOH H E [36] |
| 143 | OAc OAc αOH βOFu OAc OH αOAc βOH H E [36] |
| 144 | OAc OAc βOAc αONic OH OH H H H E [37] |
2.2. Drimane and Friedo-Drimane Sesquiterpenoids

Nitrobenzoyl drimane sesquiterpenoids are rare in natural sources, Aspergillus fungi species being the only known sources. 6β,9α-Dihydroxy-14-p-nitrobenzoylcinnamolide (145) and insulicolide A (146), insulicolide B (147), 14-O-acetylinsulicolide A (148), insulicolide C (149) and 9-deoxyinsulicolide A (150) (Figure 2) were isolated from extracts of the culture of marine-derived fungus Aspergillus ochraceus Jma1F17 [38,39]. All of them displayed significant cytotoxicity against 10 human cancer cell lines (H1975, U937, K562, BGC-823, Molt-4, MCF-7, A549, Hela, HL60, and Huh-7), with IC₅₀ values ranging from 1.95 mM to 6.35 mM, and 145 also exhibited moderate inhibitory activity against two viruses, H3N2 and EV71, with IC₅₀ values of 17.0 and 9.4 mM, respectively [38]. Compound 146 showed the strongest activities, with IC₅₀ values of 1.5, 1.5, and 0.89 μM, against ACHN, OSRC-2, and 786-O cells, respectively [39]. 148 indicated potent inhibitory activities at low μM levels, comparable to the positive control, sorafenib, a drug (Nexavar) approved for the treatment of primary kidney cancer (advanced renal cell carcinoma) [39]. Additionally, 145 and 148 exhibited stronger cytotoxicity to 786-O cells (IC₅₀ 4.3 and 2.3 μM, respectively) than to OS-RC-2 (IC₅₀ 8.2 and 5.3 μM, respectively) and ACHN (IC₅₀ 11 and 4.1 μM, respectively) [39]. Purpuride (151), berkodrimane B (152), minioluteumides A-D (153, 154, 156 and 157), purpuride B (155) (Figure 2) featuring with lactones conjugated a N-acetyl-L-valine, and such drimane sesquiterpenoid are rare in nature, which were extracted from the marine fungus, Talaromyces minioluteus (Penicillium minioluteum) [40]. Compounds 152, 153 and 157 exhibited cytotoxic activity with IC₅₀ values of 193.3, 50.6 and 57.0 μM against HepG2 cancer cell line, respectively [40]. A new sesquiterpene lactonepurpuride D (158), berkodrimane A (159), along with 151, 152, 155, 157 (Figure 2) were prepared from a culture of marine-sourced fungus Penicillium ZZ1283 in the medium of potato dextrose broth was found to have antimicrobial activities with MIC values of 4-14 μg/mL against MRSA [41]. Saccharoquinoline (160) (Figure 2) composing of a drimane-type sesquiterpene unit in combination with an apparent 6,7,8-trihydroxyquinoline-2-carboxylic acid with cytotoxicity against the HCT-116 cancer cell line by inducing G1 arrest, and was obtained from the fermentation broth of the marine-derived bacterium Saccharomonospora sp. CNQ-490 [42].

![Figure 2. The structures of compounds 145–160.](image)

Marine sponges are a rich source of bioactive secondary metabolites, the majority of which are sesquiterpene quinones/hydroquinones, most of which possess either admirane or a rearranged 4,9-friedodrimane terpenoid skeleton, which contains a C15 sesquiterpene moiety incorporating a C6 benzoquinone or hydroquinone group framework. Drimane sesquiterpene quinones represent a large group of biologically active marine natural products. Six nitrogenous drimane sesquiterpenoid aminquinones (Figure 3 and Table 2), named 18-aminoarenarone (161), 19-aminoarenarone (162), 18-methylaminoarenarone (163), 19-methylaminoarenarone (164), along with two dimeric popolohuanone F (165), popolohuanone A (166) isolated from the Australian marine sponge Dysidea sp., and 165 and 166 showed DPPH radical scavenging activity with IC₅₀ values of 35.0 and 35.0 μM, respectively [43]. A new sesquiterpene benzoaxazole, nakijinol B (167), its acetylated derivative, nakijinol B diacetate (170), and two new sesquiterpene quinones, smenospongines B (168) and C (169) (Figure 3 and Table 2), were extracted from the methanol extract of the marine sponge Dactylosponginelegans, and were found to have cytotoxic activities in the range of 1.8–46 μM against a
panel of human tumor cell lines (SF-268, H460, MCF-7, and HT-29) and a normal mammalian cell line (CHO-K1) [44]. Investigation of the marine sponge *Dysidea avara*, three bioactive sesquiterpenoid Quinones afforded, (−)-3′-methylaminoavaronane (171), (−)-4′-methylaminoavaronane (172) and (−)-N-methylmelemeleone-A (173) (Figure 3 and Table 2) with their moderate protein kinase inhibition, cytotoxicity, inhibition of NFκB-activity and insecticidal activity [45]. Two sesquiterpene aminooquinines (Figure 3 and Table 2), smenospongine (174) and glycinylilimaquinone (175), were isolated from the Fijian marine sponge *Hippopspongia* sp., and displayed lethality at LD50 = 188 and < 500 ppm against brineshrimp, respectively [46]. Bioactivity-guided isolation yielded five new sesquiterpene benzoazoles 5-epi-Nakijiquinone C–D (181 and 182) (Figure 3 and Table 2) isolated from the sponge *Dactylospogrion metachromonia* [47]. Compounds 176–180 showed potent cytotoxicity against the mouse lymphoma cell line L5178Y with IC50 values ranging from 1.1 to 3.7 μM [47]. When tested in vitro for their inhibitory potential against ALK, FAK, IGF1-R, SRC, VEGF-R2, Aurora-B, MET wt, and NEK6 kinases (IC50 0.97–8.62 μM) [47]. Dysidaminones A–M (183–195) (Figure 3 and Table 2), thirteen new sesquiterpene aminooquinines, along with six known ones (196–201), were isolated from the South China Sea sponge *Dysidea fragilis* [48]. Compounds 185, 187, 190, and 192, 196, and 198 showed cytotoxicity against mouse B16F10 melanoma and human NCI-H929 myeloma, HepG2 hepatoma, and SK-OV-3 ovarian cancer cell lines [48]. In addition, these six cytotoxic compounds also exhibited NF-κB inhibitory activity with IC50 values of 0.05–0.27 mM [48]. Four nitrogenous 4,9-friedodrimane-type sesquiterpenoids (202–205) (Figure 3 and Table 2) were acquired using the oxidative potential of *Verongularigida* on bioactive metabolites from two *Smenospongia* sponges, and the mixture of 204 and 205 suppressed β-catenin response transcription (CRT) via degrading β-catenin and exhibited cytotoxic activity on colon cancer cells [49]. Compounds 206–214, together with 174 (Figure 3 and Table 2) have been obtained from the Marine Sponge *Spongipertusa* Esper, and 174, 213, 214 exhibited activities against the human cancer cell lines U937, HeLa, and HepG2, with most potent cytotoxocities to U937 cells with IC50 values of 1.5, 2.8, and 0.6 μM, respectively [50]. Four sesquiterpene hydroquinones, dactylosphongins A–D (215–218), as well as five sesquiterpene quinones, melemeleones B–E (219–222) and dysidaminone N (223) (Figure 3 and Table 2) were isolated from the marine sponge *Dactylospongia* sp., anti-inflammatory evaluation showed that 215–218, and 223 exhibited potent inhibitory effects on the production of inflammatory cytokines (IL-6, IL-1β, IL-8, and PEG2) in LPS-induced THP-1 cells with IC50 values of 5.1–9.2 μM [51]. A new sesquiterpenoid aminooquinone nakijiquinone V (224), along with smenospongine (174) (Figure 3 and Table 2) were extracted from an Indonesian marine *Dactylospongia elegans* sponge [52]. Eleven new nitrogenous meroterpenoids, cinerols A–K (225–235) (Figure 3 and Table 2), were isolated from the marine sponge *Dysidea cinerea*, 225 and 226 feature a rare 5H-pyrrrole[1,2a]-benzimidazole moiety, while cinerols 227–231 were examples of rare meroterpene benzoazoles [53]. Six sesquiterpene quinones/hydroquinones (236–240, 210) (Figure 3 and Table 2) were acquired from the marine sponge *Dactylospongia elegans* [54]. Compounds 238–240 showed activities against the human cancer cell lines DU145, SW1990, Huh7, and PAC-1 with IC50 values ranging from 2.33 to 37.85 μM [54]. Three cytotoxic sesquiterpenoid quinones (241–243) (Figure 3 and Table 2) were purified from South China Sea sponge *Dysidea* sp., and displayed various potent cytotoxic activities with IC50 values ranging from 0.93 to 4.61 μM [55]. Two unique nitrogenous sesquiterpene quinone meroterpenoids, dysidinoid B (244) and dysicyghone A (245) (Figure 3 and Table 2) were characterized from the marine sponge *Dysideasteptosa*, and 244 exhibited significant anti-inflammatory effect by inhibiting TNF-α and IL-6 generation with IC50 values of 9.15 μM and 17.62 μM, respectively [56]. Two nitrogenous merosesquiterpene, 5-epi-nakijiquinone L (246) and 5-epi-smenospongriarine (247) (Figure 3 and Table 2) were isolated from the sponge *Verongulact.rigida* with weak 5α-reductase inhibitory activity [57].
Figure 3. The friedo-drimane sesquiterpenoids skeletons (I–XXI) and three dimers.

Table 2. Reported structures of friedo-drimane sesquiterpenoids.

| No | Name                        | R₁        | R₂           | R₃       | R₄     | R₅     | R₆     | R₇     | Type | Ref |
|----|-----------------------------|-----------|--------------|----------|--------|--------|--------|--------|------|-----|
| 161| 18-Aminoarenarone           | H         | NH₂          | H        | αH     | αCH₂   | βCH₂   | βCH₂   | I    | [43]|
| 162| 19-Aminoarenarone           | NH₃       | H            | H        | αH     | αCH₂   | βCH₂   | βCH₂   | I    | [43]|
| 163| 18-Methylaminoarenarone     | H         | NHCH₃        | H        | αH     | αCH₂   | βCH₂   | βCH₂   | I    | [43]|
| 164| 19-Methylaminoarenarone     | NHCH₃     | H            | H        | αH     | αCH₂   | βCH₂   | βCH₂   | I    | [43]|
| 167| Nkijinol B                  | OH        | OH           | H        | H      | βCH₂   | βCH₂   | βCH₂   | II   | [44]|
| 168| Smenospongine B             | H         | NHCH₂COOH    | OH       | αH     | βCH₂   | βCH₂   | βCH₂   | I    | [44]|
| 169| Smenospongine C             | H         | NH(CH₃)₂COOH | OH       | H      | βCH₂   | βCH₂   | βCH₂   | II   | [44]|
| 170| Nkijinol B diacetate        | OAc       | OAc          | H        | H      | βCH₂   | βCH₂   | βCH₂   | I    | [44]|
| 171| (−)-3′-Methylaminoavarone   | H         | NHCH₂        | H        | αH     | βCH₂   | βCH₂   | βCH₂   | III  | [45]|
| 172 | (-)-4'-Methylaminoavarone | NHCH₃ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [45] |
| 173 | (-)-N-Methylmelemeleone-A | H | N(CH₃)(CH₃)₂SO₂H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [45] |
| 174 | Smenosponge | H | NH₂ | OH | αH | βCH₃ | βCH₃ | βCH₃ | IV [46,50,52] |
| 175 | Glycymilimaquinone | H | NHCH₂COOH | OH | αH | βCH₃ | βCH₃ | βCH₃ | IV [46] |
| 176 | 5-epi-Nakijiquinone S | H | | | OH | αH | αCH₃ | βCH₃ | βCH₃ | V [47] |
| 177 | 5-epi-Nakijiquinone Q | H | | | OH | αH | αCH₃ | βCH₃ | βCH₃ | V [47] |
| 178 | 5-epi-Nakijiquinone T | H | | | OH | αH | αCH₃ | βCH₃ | βCH₃ | V [47] |
| 179 | 5-epi-Nakijiquinone U | H | NH(CH₃)₂SCH₃ | OH | αH | αCH₃ | βCH₃ | βCH₃ | V [47] |
| 180 | 5-epi-Nakijiquinone N | H | N(CH₃)(CH₃)₂CH₂ | OH | αH | αCH₃ | βCH₃ | βCH₃ | V [47] |
| 181 | 5-epi-Nakijinol C | OH | OCH₃ | CH₃ | αH | αCH₃ | βCH₃ | βCH₃ | VI [47] |
| 182 | 5-epi-Nakijinol D | CH₃ | CH₃ | - | αH | αCH₃ | βCH₃ | βCH₃ | VII [47] |
| 183 | Dysidaminone A | NHCH₂CH₂CH₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 184 | Dysidaminone B | NHCH₂CH₂CH₂CH₂CH₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 185 | Dysidaminone C | H | N(CH₃)₂ | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 186 | Dysidaminone D | N(CH₃)₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 187 | Dysidaminone E | H | NHCH₂CH₂CH₂ | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 188 | Dysidaminone F | H | NHCH₂CH₂CH₂CH₂ | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 189 | Dysidaminone G | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 190 | Dysidaminone H | H | NHCH₃ | H | αH | βCH₃ | βCH₃ | βCH₃ | I [48] |
| 191 | Dysidaminone I | NHCH₃ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | I [48] |
| 192 | Dysidaminone J | H | N(CH₃)₂ | H | αH | βCH₃ | βCH₃ | βCH₃ | I [48] |
| 193 | Dysidaminone K | NHCH₂CH₂CH₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | I [48] |
| 194 | Dysidaminone L | NHCH₂CH₂CH₂CH₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | I [48] |
| 195 | Dysidaminone M | H | H | αH | βCH₃ | βCH₃ | βCH₃ | I [48] |
| 196 | 18-Methylaminoavarone | H | NHCH₃ | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 197 | 19-Methylaminoavarone | NHCH₃ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 198 | 18-Aminoavarone | H | NH₂ | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 199 | 19-Aminoavarone | NH₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| 200 | 18-Phenethylaminoavarone | H | | | | H | αH | βCH₃ | βCH₃ | βCH₃ | III [48] |
| Compound                                | Structure     | Chemical Formula | Description                                      |
|-----------------------------------------|---------------|------------------|-------------------------------------------------|
| Popolohuanone D                         | ![structure](image) | CH<sub>2</sub>OH |                                  |
| (-)-Nakijinol E                         | H             | CH<sub>3</sub>OH |                                |
| (+)-5-epi-Nakijinol E                   | H             | CH<sub>3</sub>OH |                                |
| Nakijinone A                            | H             | CH<sub>3</sub>OH |                                |
| 5-epi-Nakijinone A                      | H             | CH<sub>3</sub>OH |                                |
| 18-Deoxy-18-formamidodictyocerin B      | H             | NHCHO            |                                |
| 18-Deoxy-18-(2-hydroxyacetyl)aminodictyocerin B | H             | NHCHO            |                                |
| N-Methyl-ent-smenosponge D              | H             | NHCHO            |                                |
| N-Methyl-5-epi-smenosponge D            | H             | NHCHO            |                                |
| 20-Demethoxy-20-methylaminodactyloquinone D | H         | NHCHO            |                                |
| 20-Demethoxy-20-methylaminodactyloquinone D | H         | NHCHO            |                                |
| 5-epi-Smenosponge D                     | H             | NH<sub>2</sub>    |                                |
| Smenospongidiene                        | H             | NHCH<sub>3</sub>|                                |
| Dactylospongin A                        | H             | OH               |                                |
| Dactylospongin B                        | H             | OH               |                                |
| Dactylospongin C                        | H             | NHCHO            |                                |
| Dactylospongin D                        | H             | NHCHO            |                                |
| ent-Melemeleone B                       | H             | NHCH<sub>3</sub>SOH |                            |
| Melemeleone C                           | H             | NHCH<sub>3</sub>SOH |                            |
| Melemeleone D                           | H             | NHCH<sub>3</sub>SOH |                            |
| Melemeleone E                           | H             | NHCH<sub>3</sub>SOH |                            |
| Dysidaminone N                          | H             | NH               |                                |
| Nakijiquinone V                         | H             | OH               |                                |
| Cinerol A                               | H             | OH               |                                |
| Cinerol B                               | H             | OH               |                                |
| Cinerol C                               | H             | OH               |                                |
| Cinerol D                               | H             | OH               |                                |
| 229 | Cinerol E | H | OH | H | CH₃ | βCH₃ | βCH₃ | βCH₃ | II | [53] |
| 230 | Cinerol F | H | OH | H | αH | βCH₃ | βCH₃ | βCH₃ | XIX | [53] |
| 231 | Cinerol G | H | OH | CH₃ | αH | βCH₃ | βCH₃ | βCH₃ | XIX | [53] |
| 232 | Cinerol H | H | H | αH | βCH₃ | βCH₃ | βCH₃ | XIV | [53] |
| 233 | Cinerol I | H | H | αH | βCH₃ | βCH₃ | βCH₃ | XIV | [53] |
| 234 | Cinerol J | NHCHO | H | H | αH | βCH₃ | βCH₃ | βCH₃ | XIV | [53] |
| 235 | Cinerol K | NHCOCH₂CH(CH₃)₂ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | XIV | [53] |
| 236 | 20-Demethoxy-20-isopentylaminodactyloquinone D | H | NH(CH₃)₂CH(CH₃)₂ | - | αH | βCH₃ | βCH₃ | βCH₃ | X | [54] |
| 237 | 20-Demethoxy-20-isobutylaminodactyloquinone D | H | NHCH₂CH(CH₃)₂ | - | αH | βCH₃ | βCH₃ | βCH₃ | X | [54] |
| 238 | Smenospongiarine | H | NH(CH₃)₂CH(CH₃)₂ | OH | βH | αCH₃ | αCH₃ | αCH₃ | I | [54] |
| 239 | Smenospongorine | H | NHCH₂CH(CH₃)₂ | OH | βH | αCH₃ | αCH₃ | αCH₃ | I | [54] |
| 240 | Smenospongimine | H | NHCH₂ | OH | βH | αCH₃ | αCH₃ | αCH₃ | I | [54] |
| 241 | (+)-19-Methylaminoavarone | NHCH₃ | H | H | αH | βCH₃ | βCH₃ | βCH₃ | V | [55] |
| 242 | (−)-20-Phenethylaminoavarone | H | NHCH₃ | H | αH | βCH₃ | βCH₃ | βCH₃ | V | [55] |
| 243 | (−)-20-Methylaminoavarone | H | NHCH₃ | H | αH | βCH₃ | βCH₃ | βCH₃ | V | [55] |
| 244 | Dysidinoid B | H | H | - | αH | βCH₃ | βCH₃ | βCH₃ | XX | [56] |
| 245 | Dysicigyhone A | H | OH | CH₃ | αH | βCH₃ | βCH₃ | βCH₃ | XXI | [56] |
| 246 | 5-epi-Nakijiquinone L | H | NHCH₂CH(CH₃)CH₂CH₃ | OH | αH | αCH₃ | βCH₃ | βCH₃ | IV | [57] |
| 247 | 5-epi-Smenospongiarine | H | NH(CH₃)₂CH(CH₃)₂ | OH | αH | αCH₃ | βCH₃ | βCH₃ | IV | [57] |
Drimane sesquiterpenoid-indole alkaloids rarely occur in Nature. Only eight compounds were isolated from actinomycete *Streptomyces* sp. Three hybrid isoprenoid drimane derivatives—indotertine A (248), drimentine F (249) and drimentine G (250) (Figure 4)—were afforded from a reed rhizosphere soil-derived actinomycete *Streptomyces* sp. CHQ-64 [58]. Compound 250 showed strong cytotoxicity against human cancer cells lines with IC₅₀ values down to 1.01 μM, while 248 and 249 showed no significant activity [58]. Four new indolo-drimanesesquiterpenes, dixiamycins A (251) and B (252), oxiamycin (253), and chloroxiamycin (254), were isolated from a marine-derived actinomycete *Streptomyces* sp. and characterized, together with the known compound xiamycin A (255) (Figure 4) [59]. 251 and 252 are the first examples of atropisomerism of naturally occurring N–N coupled atropo-diastereomers, with a dimeric indolo-sesquiterpene skeleton and a stereogenic N–N axis between sp²-hybridized nitrogen atoms [59]. The two dimeric compounds 251 and 252 showed better antibacterial activities than the monomers 253–255 with the IC₅₀ values of 4–16 μg/mL against four indicator strains (*Escherichia coli* ATCC25922, *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* SCSIO BS01 and *Bacillus thuringiensis* SCSIO BT01) [59].

![Figure 4. The structures of compounds 248–255.](image)

### 2.3. Eudesmane Sesquiterpenoids

Eleven nitrogen-containing eudesmane sesquiterpenoids, halichonadins G–Q (256–266) (Figure 5), were isolated from a marine sponge *Halichondrias* and compounds 256 and 258 showed cytotoxicity against murine lymphoma L1210 cells (IC₅₀ 5.9 and 6.9 μg/mL) and human epidermoid carcinoma KB cells (IC₅₀ 6.7 and 3.4 μg/mL) in vitro, Halichonadin K showed cytotoxicity against human epidermoid carcinoma KB cells (IC₅₀ 10.6 μg/mL) in vitro, and halichonadin O displayed antimicrobial activity against *Staphylococcus aureus* (MIC 8 μg/mL), *Micrococcus luteus* (MIC 8 μg/mL), and *Trichophyton mentagrophytes* (IC₅₀ 16 μg/mL) [60–62]. One eudesmane-type sesquiterpene, phaeusmane I (267) (Figure 5), was isolated from the rhizomes of *Curcumaphaeocaulis* [63]. Three new nitrogen-containing sesquiterpenoids, the cespilamides C–E (268–270, Figure 5) were purified from the Taiwanese soft coral *Cespitularia taeniata*, and 270 exhibited cytotoxicity against human breast adenocarcinoma (MCF-7), medulloblastoma (Daoy), and cervical epithelial carcinoma (Hela) cancer cells with IC₅₀ of 17.5, 22.3, and 24.7 μM, respectively [64]. Acanthine B (271), acanthine C (272), 11-isocyanato-7βH-eudesm-5-ene (273), 11-isothiocyanato-7βH-eudesm-5-ene (274), and 11-formamido-7βH-eudesm-5-ene (275) (Figure 5) were isolated from the Thai sponge *Halichondrias* [65]. Four new uncommon nitrogenous eudesmane-type sesquiterpenes, axiriabilines A–D (276–279), and one
known related ent-stylotelline (280) (Figure 5), were isolated from the Hainan sponge *Axinysavaraiabilis* with no cytotoxicity against several cancer cells [66]. Axirabiline A (276) and 11-formamido-7βH-eudesm-5-ene (281) (Figure 5) were extracted from South China Sea Nudibranchs *Phyllidiellasp* [67]. Spiroalanpyrroids A (282) and B (283), two sesquiterpene alkaloids with an unprecedented eudesmanolide-pyrrolizidine spiro [55] framework, were isolated together with two new sesquiterpene-amino acid adducts, helenalanprolines A (284) and B (285) (Figure 5), from the roots of *Inula helenium* [68]. Bioassays showed that 284 and 285 significantly inhibited nitric oxide production in lipopolysaccharide-induced RAW 264.7 macrophages with IC₅₀ values of 15.8 and 13.5 μM, respectively [68].

![Figure 5. The structures of compounds 256-285.](image)

### 2.4. Cadinene Sesquiterpenoids

Two nitrogenous cadinene sesquiterpenes (3S*, 5R*, 6R*, 9R*)-3-formamido-1(10)-cadinene (286) and (−)-halichamine (287) (Figure 6) were isolated from the Thai marine sponge *Halichondriasp* [69]. Compound 286 showed moderate cytotoxic activity against HeLa, MOLT-3, and HepG2 cell lines with IC₅₀ values of 32.1, 33.4, and 16.0 mM, respectively, while compound 287 also displayed moderate cytotoxic activity against HuCCA-1, MOLT-3, HepG2, and MDA-MB231 cell lines with IC₅₀ values of 20.3, 34.6, 19.9, and 22.6 mM, respectively [69]. (1R, 6S, 7S, 10S)-10-isothiocyanatocadine (288), axinosothiocyanate J (289) (Figure 6) were extracted from the marine sponge *Axinysasp* [70]. Halichon C (290) and 4-epihalichon C (291), halichon D (292), halichonG (293), (−)-10-isocyano-4-cadinene (294), and (−)-10-isothiocyanato-4-cadinene (295) (Figure 6), were obtained from the Thai sponge *Halichondriasp* [65]. Compounds 290, 291, and 294 exhibited moderate cytotoxicity (IC₅₀ 20.9, 29.0, and 9.1 μM, respectively) against the MOLT-3 cell line and compound 292 also showed moderate cytotoxicity against HepG2 and MDA-MB231 cell lines with IC₅₀ values of 24.3 and 19.3 μM, respectively [65]. New stereoisomers of (−)-(1S*, 4S*, 6S*, 7R*)-4-isocyano-9-amphorine (296) and of (−)-(1S*, 6R*, 7R*, 10S*)-10-isocyano-4-amphorine (297), 4α-isocyano-9-amphorine (298), (1S*, 4S*, 6S*, 7R*)-4-thiocyanato-9-cadinene (299), (−)-10-isocyano-4-amphorine (300), (−)-10-isothiocyanato-4-cadinene (301) (Figure 6), were identified from *Phylidiella pustulosa* and from *Phylidiaceollata* [71]. A novel sesquiterpenoidal lactam, commiphocolactam A (302) (Figure 6) was isolated from *Resinacommiphora* [72]. Biological assessment against human cancer cells showed that the IC₅₀ values of 302 against HepG2 and A549 cells were 21.73 μM and 128.50 μM, respectively [72]. Axidosothiocyanate A (303), 10-isothiocyanato-4-cadinene (304), 10-formamido-4-cadinene (305), along with 289, 293 (Figure 6), were identified from two South China Sea Nudibranchs *Phylidiella pustulosa, Phyllidiaceolesis* [67].
2.5. Bisabolane Sesquiterpenoids

Brasilamides E–J (306–311), bisabolane sesquiterpenoids with 3-cyclohexylfuran (306 and 307) and 3-cyclohexylfuranone (308–311) skeletons (Figure 7), were isolated from scaled-up fermentation cultures of the plant endophytic fungus Paraconiothyrium brasiliense Verkley [73]. Compound 307 selectively inhibited the proliferation of the breast (MCF-7) and gastric (MGC) cancer cell lines, with IC₅₀ values of 8.4 and 14.7 μM, respectively [73]. N,N′-bis[6R,7S]-7-amino-7,8-dihydro-a-bisabolone-7-yl]urea (304), and (6R,7S)-7-amino-7,8-dihydro-α-bisabolene (313) (Figure 7), were purified from the marine sponge Axinyssa sp. collected at Iriomote Island [70]. Compound 312 was the most potent inhibitor of PTP1B activity (IC₅₀ = 1.9 μM) without cytotoxicity at 50 μM in two human cancer cell lines, hepatoma Huh-7 and bladder carcinoma EJ-1 cells [70]. Compound 312 also moderately enhanced the insulin-stimulated phosphorylation levels of Aktin Huh-7 cells [70]. D⁸¹⁴,3-isocyanototheonellin (314) and 3-isocyanototheonellin (315), theonellin formamide (316), theonellin isothiocyanate (317), and 7-isocyno-7,8-dihydro-α-bisabolene (318) (Figure 7) were extracted from the two South China Sea nudibranchs Phyllidiellapustulosa and Phyllidiacoelotis [67]. Compounds 315, 317, and 318 exhibited strong cytotoxicity against human cancer cell line SNU-398 with IC₅₀ values of 0.50, 2.15, and 0.50 μM, respectively [67]. In addition, compound 315 also displayed broad cytotoxicity against the other three cancer cell lines, including A549, HT-29, and Capan-1, with IC₅₀ values of 8.60, 3.35, and 1.98 μM, respectively [67]. A rearranged bisabolene-type sesquiterpene, halichonic acid (319), was isolated from a marine sponge Halichondria sp., together with 313 [74] (Figure 7). Compound 313 was cytotoxic against HeLa cells with an IC₅₀ value of 50 μM, whereas 314 did not show cytotoxicity even at 50 μM [74]. Five novel highly oxygenated norbisabolane sesquiterpenes, namely phyllanthacidoid U (320), phyllanthacidoid A (321), phyllanthacidoid B (322), phyllanthacidoid L (323), and phyllanthacidoid S (324) (Figure 7) were isolated from the roots and stems of Phyllanthus acidus, and compounds 321–323 displayed potential anti hepatitis B virus (anti-HBV) activities [75].
2.6. Germacrene, Elemene and Iresane Sesquiterpenoids

Two germacrene-type sesquiterpenoid dimers—obisparthenolidone (325) and bisparthenolidone (326) (Figure 8) were isolated from the chloroform-soluble fraction of the methanolic extract of the bark of *Magnolia kobus* (Magnoliaceae) [76]. Compound 325 displayed broad cytotoxicity against four cancer cell lines, including A549, SK-OV-3, SK-MEL-2, and HCT-15, with IC\textsubscript{50} values of 2.0, 1.9, 3.9 and 3.2 μM, respectively [76]. Novelresane sesquiterpene alkaloids, halichonines A (327), B (328), and C (329) (Figure 8), were identified from the marine sponge *Halichondriakadai* Kadota, and 328 was then subjected to the trypan blue dye exclusion using HL60 human leukemia cells, and showed cytotoxicity (IC\textsubscript{50} value: 0.60 μg/ml) [77]. One γ-elemene-type sesquiterpenes, 8β(H)-elema-1,3,7(11)-trien-8,12-lactam (330) (Figure 8) was obtained from the rhizomes of *Curcuma phaeocaulis* [63]. Three new germacrene sesquiterpenoid-type alkaloids with an unusual Δ\textsuperscript{7,12}-lactam moiety, glechomanamides A–C (331–333) (Figure 8) were isolated from *Salvia capensisformis* [78]. In a tube formation assay, 332 showed the most potent antiangiogenic activity in primary screening, and its IC\textsubscript{50} value was determined to be 40.4 μM [78]. In addition to VEGFR2, 332 decreased BMP4 expression, which regulates tube formation, and glycolysis-related proteins, including GLUT1 and HK2, which suggests that the novel compound 332 is worthy of additional investigation for angiogenesis-associated pathological conditions [78]. Onoporoids A–D (334–337) (Figure 8), three elemences and one germacrine, were extracted from the whole aerial parts of *Onopordumalexandrinum*, which possess unique structures combining a sesquiterpenoid framework with an amino acid, L-proline [79].

2.7. Farnesane, Spiroaxane, Aromadendrane and Pupukeanene Sesquiterpenoids

Chemical investigation of the endophytic fungus *Emericella* sp. (HK-ZJ) isolated from the mangrove plant *Aegicerascornicum* led to the isolation of six farnesane sesquiterpenoids named emeriphenolicins A–F (338–343) (Figure 9) with moderate anti-influenza A viral (H1N1) activities [80]. An unusual farnesane natural product (dotofide, 344) (Figure 9), in which the terpenoid skeleton is interrupted by a guanidine moiety was obtained from the marine slug *Doto pinmatiida* [81]. Two spiroaxane sesquiterpenes, (−)-axisonitrile-3 (345), (+)-axamide-3 (346), and one aromadendrane sesquiterpene axamide-2 (347) (Figure 9) were isolated from the Thai marine sponge *Halichondriadsp*, and only 345 showed strong activity to the HepG2 cell line with an IC\textsubscript{50} value of 1.3 μM [69]. Fasciospyrinadine (348) (Figure 9), a novel farnesane sesquiterpene pyridine alkaloid was extracted from Guangxi sponge *Fasciospongiasp* [82].

![Chemical structures](image-url)
Apupukeanane-type sesquiterpenoid isomers, 9-thiocyanatopupukeanane isomers (349–350) (Figure 9) were isolated from the Thai sponge Halichondrias [65]. A bioassay-guided phytochemical study was conducted on the semi-mangrove plant Myoporum bontioides. A. Gray, which led to the isolation of two new farnesane sesquiterpene alkaloids, myoporunes A (351) and B (352) (Figure 9), which displayed potent anti-MRSA activity with MIC value of 6.25 μg/mL [83]. Two aromadendrane sesquiterpene 1-isothiocyanatoaromadendrane (353) and 347, one spioaxane-type sesquiterpenoid axamide-3 (354), and two pupukeanane-type sesquiterpenoids (349, 350) (Figure 9), were isolated from the nudibranchs Phyllidiellapustulosa and Phyllidiaceoestis [67].

Figure 8. The structures of compounds 325-337.

Figure 9. The structures of compounds 338–354.
2.8. Tremulane, Daucane, Brasilane, Salvia\-lane, Aristolane, Bergamotane and Valerane Sesquiterpenoids

Huptremules A–D (compounds 355–358) (Figure 10) featuring unusual sesquiterpenoid-alkaloid hybrid structures that integrate the characteristics of fungal metabolites (tremulane sesquiterpenoids) and the exogenous substrate, were isolated from a fungal endophyte of *Huperzia serrata* [84]. Compound 355–358 selectively inhibited acetylcholinesterase activities, with IC\(_{50}\) values of 0.99, 2.17, 0.11 and 0.06 \(\mu\text{M}\), respectively [84]. Two daucane-type sesquiterpenoids, aculene\(\text{A} (359)\) and B (360) (Figure 10), were identified from *Aspergillus aculeatus*, which were tested for antifungal activity against *Candida albicans*. However, all showed only weak or no activity [85]. One brasilane-type sesquiterpenoid, named diaporol L (361) (Figure 10) was isolated from *Diaporthe* sp., an endophytic fungus associated with the leaves of *Rhizophorastylosa* collected in Hainan Province, China [86]. One salvialane-type sesquiterpene halichon E (362) and one aristolane sesquiterpene epipolasin A (363) (Figure 10) were obtained from the Thai sponge *Halichondria* sp. [65]. Sporulaminals A (364) and B (365) (Figure 10), a pair of unusual epimericspiroaminal derivatives, bearing 6/4/5/5 tetracyclic ring system derived from bergamotane sesquiterpenoid, were isolated from a marine-derived fungus *Paraconiothyrium* sporulosum YK-03 [87]. Volvalerine A (366) (Figure 10), a novel \(N\)-containing valerane bisesquiterpenoid derivative with a dihydroisoxazole ring, was isolated from the roots of *Valeriana officinalis* var. *latifolia* [88]. Compound 366 was also evaluated for their enhancing activity on NGF mediated neurite outgrowth in PC12 cells. The result indicated that the proportion of the NGF-induced neurite-bearing cells (with NGF 5 ng/mL) was not enhanced by compound 366 at 50 \(\mu\text{M}\) [88].

![Figure 10. The structures of compounds 355–366.](image)

2.9. Cyclonerane, Axane, Nardosinane, Zizaane, Eremophilane, and Guaiane Sesquiterpenoids

The nitrogenous cycloneranonesesquiterpenescyclonerin A (367) and B (368) along with seven new congeners—deoxycyclonerins A–D (369–372), cyclonerinal (373), and cyclonerizole (374) (Figure 11)—were isolated from the culture of a marine algicolous strain (A-YMD-9-2) of *Trichoderma asperellum* [89]. And, compounds (367–374) showed significant cytotoxic activity against harmful microalgae Chattonella marina with the IC\(_{50}\) value of 2.1–30 \(\mu\text{g/mL}\) [89]. Antartin (375) (Figure 11), a cytotoxic zizaane-type sesquiterpenoid was obtained from a *Streptomyces* sp. SCO736, isolated from an Antarcticmarine sediment, and showed cytotoxicity against A549, H1299, and U87 cancer cell lines by causing cell cycle arrest at the G1 phase [90]. One eremophilane sesquiterpene dendryphiellin J
(376) (Figure 11) was isolated from the marine-derived fungus Cochliobolus lunatus SCSIO41401 [91]. Compound 376, a rare naturally occurring aldoxime analogue, displayed cytotoxicities against ACHN and HepG-2 cells with IC$_{50}$ values of 3.1 and 5.9 μM, respectively [91]. One unusual sesquiterpenoid dimer, nardochinoid B (377) (Figure 11) was isolated from Nardostachys chinensis Batal [92]. Compound 377 is the first nitrogen-containing nornardosinane-aristolane sesquiterpene conjugate. The ED$_{50}$ of compound 377 on the production of NO was 5.73, and obviously inhibited LPS-induced iNOS and COX-2 protein expression in a dose-dependent way, and increased HO-1 protein expression at the concentration of 10 μM [92]. Three axane sesquiterpenoid isonitrile picaaisonitrile-1 (378), picaisonitrile-2 (379), and cavernothiocyanate (380) (Figure 11) were extracted from hyllidiapicta collected from Bali, Indonesia [71]. Vlasouamine A (381) (Figure 11), an unprecedented guaiane sesquiterpene lactone dimer featuring a fully hydrogenated pyrrolo[2,1,5-cd] indolizine core, was isolated from the roots of Vladimiriasouliei [93]. Moreover, 381 exhibited neuroprotective activity when evaluated for glutamate-induced cytotoxicity, nuclear Hoechst 33,258 staining, and measuring intracellular reactive oxygen species levels, using a rat pheochromocytoma PC12 cell-based model system [93]. Clavukoellians A–D (382–385) (Figure 11), highly rearranged nardosinane Sesquiterpenoids with antiangiogenic activity were purified from the marine soft coral Clavulariakoellikeri [94]. Compound 382 has a unique skeleton with both lactone and maleimide ring systems, which is rare in natural products, and appears to be formed by oxidase cleavage of the C-7/C-8 bond of a nardosinane precursor with inhibiting the migration of the human umbilical vein endothelial cells (HUVECs) at 2.5 μM [94].

![Figure 11. The structures of compounds 367–385.](image)

2.10. Others

Five sesquiterpene isocyanides, isothiocyanates, thiocyanates, and formamides—halichon A (386), halichon B (387), halichon F (388), halichon H (389), and (+)-2-thiocyanatoneopuukeanane (390) (Figure 12) — were isolated from the Thai sponge Halichondriasp [65]. Lamellodysidine B (391) (Figure 12), a sesquiterpenes isolated from the marine sponge Lamellodysideatheracea, collected in Indonesia.
[95]. Biological activities of 391 was tested in our in-house screening including cytotoxicity, antimicrobial activities, inhibitory activity of the cholesterol ester accumulation in macrophages, inhibitory activity of the RANKL-induced formation of multinuclear osteoclasts, and inhibitory activities of the ubiquitin-proteasome system (proteasome, E1, Ubc13 (E2)–Uev1A interaction, p53-Mdm2 (E3) interaction, and USP7). However, no significant activity was detected for the compound [95].

![Image 81x610 to 87x616](image1)

**Figure 12.** The structures of compounds 386–391.

3. Occurrence

Natural nitrogenous sesquiterpenoids are mainly distributed in species of plants belonging to the Celastraceae, Saxifragaceae, Zingiberaceae, Asteraceae, Burseraceae, Phyllanthaceae, Magnoliaceae, Lamiaceae, Myoporaceae, and Valerianaceae families, marine sponges belonging to the Dysidea, Thorectidae, Spongidae, and Halichondra families, soft corals belonging to the Xenia and Clavularia families, phyllid nudibranchs belonging to the Phyllidiidae family, marine slugs belonging to the Dotidae family), fungi belonging to the Trichocomaceae, Eurotiaceae, Parmulariaceae, Phanerochaetaceae, Diaporthaceae, and Pezizaceae families, bacteria belonging to the Pseudomonadaceae family, and actinomycyes belonging to the Streptomycetaceae family (Table 3). Dihydroagarofuran sesquiterpenoids have been isolated from the roots of Maytenusmekongensis, the stems of M. oblongata, the leaves of M. spinosa, the roots and leaves of Tripterygium wilfordii, the stems of T. regelii, the root barks of T. hypoglaucum, the seeds of Celastrusorbiculatus, the seeds of C. paniculatus, the stems of Euonymus alatus, the whole plants of Parnassiatwightiana, the leaves of Montinapetalumchinense. Friedo-drimane and drimane sesquiterpenes have been isolated from maring sponges of the following species: Dysidea, D. avara, D. fragilis, D. cinerea, D. septosa, Dactylospongia, D. elegans, and D. metachromia. Drimane sesquiterpenoids have been purified from the fungi Aspergillussochaceus, A. aculeatus, Talaromyces minioluteus, and Penicillium sp. ZZ1283, the bacterium Saccharomonospora sp. CNQ-490, and the actinomycete Streptomyces. Eudesmanesesquiterpenoids have been identified in marine sponges of Halichondria sp., H. okadaii, Axinyssasp., and A. variabilis, the soft coral Cespitulariaeniata, phyllid nudibranchs of the Phyllidiella sp., P. putulsora, and P. ocellate species and the plants Curcumaphaeocaulis and Inula heleniun. L. Germanacine squiterpenoids were isolated from the plants Onopordumalexandrinum, Magnolia kobus, and Salvia scapiformis. Cadinane sesquiterpenes were extracted from the plant Resinacomphilora, marine sponges like Halichondria sp. and Axinyssasp., phyllid nudibranchs of the Phyllidiella and Bisabolane sesquiterpenoids have been isolated from Phyllanthus acidus (L.) skeels, Halichondria sp. Phyllidiella sp., Paraconiothyniumbrasiliense and P. sporulosum.

| Classification | Family    | Species                        | Type                | Reference           |
|----------------|-----------|--------------------------------|---------------------|---------------------|
| Plant          | Celastraceae | Maytenusmekongensis; M. spinosa; M. oblongata | Dihydroagarofuran | [17,25,30]          |
|                |           | Tripterygium wilfordii; T. regelii; T. hypoglaucum |                     |                     |

Table 3. The species containing nitrogenous sesquiterpenoids.
| Molecules 2020, 25, 2485 |
|--------------------------|
| [19,34,37] Celastrusorbiculatus; C. angulatus; C. paniculatus Euvynxus alatus Monimopetalumchinense |
| [22] Saxifragaceae Parnassia wightiana |
| [27] Zingiberaceae Curcuma phaeoocallis Euonymus alatus |
| [35] Asteraceae Inula helemium L. Onopordumalexandrinum |
| [37] Burseraceae Vladimirasouliei Resinacommiphora |
| [22] Phyllanthaceae Phyllanthus acidus(L.) skels Eudesmane; Elemene |
| [75] Magnoliaceae Magnolia kobus Germacrane; Elemene |
| [83] Lamiaceae Salvia scapiformis Germacrane |
| [72] Myoporaceae Myoporum bontioides Germacrane |
| [88] Valerianaceae Valeriana officinalis var. latifolia Nomarostachyschinensis |
| [78] Dyeidea sp.; D. avara; D. fragilis; D. cinerea; D. septosa |
| [53,55,56] Dysidea; Dactylosphorgia sp.; D. elegans; D. metachromia |
| [43,45,48,53,55,56] Thorectidae Smenospongia aurea, S. cerebriformis, and Verongularigida |
| [44,47,51,52,54] Sponge Spongiapertusa Esper |
| [46] Soft coral Halichondriidae Halichondriidae |
| [50] Phyllididae Phyllidiella sp.; P. pustulosa; P. ocellata |
| [66,70] Phyllidae | Eudesmane; Cadinane; Bisabolane; Aromadendrane; Pupukeane; Salvialane; Aristolone; Iresane |
| [82] Thorectidae Fasciospongia sp. Farnesane |
| [64] Xeniidae Cespitulariataeniata Eudesmane |
| [94] Soft coral Clarulariakoellikeri Nardosinane |
| [60–62,65,69,74,77] Marine slug Doto pinnatifida Farnesane |
| [81] Phyllididae Phyllidiella sp.; P. pustulosa; P. ocellata |
| [38,39,85] Fungus Trichocomaceae Aspergillus ochraceus; A. aculeatus Talaromyceseminoliuteus |
| [40] | Drimane; Daucane |
4. Conclusions

In summary, a total of 391 bioactive nitrogenous sesquiterpenoids have been isolated and characterized from plants, microorganisms, and marine organisms at the past ten years. This report systematically describes the occurrence, isolation, structures and biological activities of these nearly 400 natural products that contain a nitrogen-carbon/nitrogen-nitrogen/nitrogen-sulfur bond. These natural products are dispersed over several structural classes, isolated from many different sources (both marine and terrestrial) and possess a diverse array of biological activities. It can be concluded that the structure types are obviously related to the species sources, and the bioactivities of nitrogenous sesquiterpenoids are obviously related to structure types, being particularly important their cytotoxic activities. The important points arising from this review are the following: (1) There are few structural types of N-containing sesquiterpenes in plants, while the structural types of sesquiterpenes with nitrogen in marine resources and microorganisms are various and diverse. (2) Dihydroagarofuran sesquiterpenoids were considered the most widespread and characteristic metabolites of the plants of Celastraceae, which are well recognized as characteristic metabolites and important chemotaxonomic markers or indicators of the family, except for some β-dihydroagarofurans obtained from the Saxifragaceae species Parnassia wightiana. (3) Sponges and their associated microorganisms are the largest contributors of nitrogenous sesquiterpenoids. Rearranged 4,9-friedo-drimaneterpenoid skeletons represent the majority of nitrogen-containing sesquiterpenes isolated from marine sponges. The types of sesquiterpenoids that are the most abundant among the marine organisms, Halichondria sp. (spponge) and Phyllidiella sp. (nudibranchs), are all sesquiterpene isocyanides, isothiocyanates, thiocyanates, and formamides. (4) Nitrogenous sesquiterpenes are rich in microorganisms, such as fungus, bacteria and actinomycetes and the main skeleton types are drimane, bisabolane, farnesane, tremulane sesquiterpenoids and so on. (5) Dihydroagarofuran sesquiterpenoids show significant anti-inflammatory, neuroprotective, and immunosuppressive effects, while sesquiterpenes isolated from marine organisms exhibit remarkable antitumor cytotoxic activities. Due to the rich activities and structural diversity of N-containing sesquiterpenes, researchers have not stopped exploring and studying such compounds. We hope this review will stimulate further research into this interesting class of nitrogenous secondary metabolites.

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Abbreviations

- OAc
- OBz
- OFu
- ONic
- OtCin
- OcCin
- OTig
- OMeBut

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