Diterpenes From the Marine Brown Algae of the Genus *Dilophus*

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Abstract

Brown algae of the genus *Dilophus* contain plenty of biologically active secondary metabolites with diverse structures. Excellent progress has been made in the discovery of diterpenes with extensive chemical defense activity from this genus. Most of these diterpenes exhibit significant biological activities, such as antifungal, cytotoxic, and feeding-deterrent activities. In the present review, we summarized diterpenes isolated from the brown algae of the genus *Dilophus*.

Keywords

*Dilophus*, diterpenes, secondary metabolites, synthesis, bioactivity

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Diterpenes are a group of natural products derived from both terrestrial and marine organisms. Some diterpenes, including paclitaxel, andrographolide, and ginkgolide, have been widely used in clinical practice due to their remarkable pharmacological activities. In the past few decades, excellent progress has been made in the discovery of marine diterpenes with diverse chemical structures. Previous studies have proved that marine brown algae of the family Dictyotaceae are excellent sources of bioactive secondary metabolites with diverse structural features. Some Dictyotaceae diterpenes are of chemosystematic value. Biogenetic considerations allow us to subdivide some Dictyotaceae diterpenes into 3 groups, depending on the first cyclization of the common geranylgeraniol precursor. While other Dictyotaceae diterpenes, including cubebane-style diterpenes, have not been discussed in the literature (Figure 1). The genus *Dilophus* is the most representative genus of the family, and chemotaxonomic studies of diterpenes from the genus *Dilophus* have been reported.

Species of the genus *Dilophus* are mainly distributed in the tropical zone of the world. *Dilophus*, a genus closely related to *Dictyota*, consists of species producing prolific bioactive secondary metabolites. At present, hundreds of natural bioactive products, including terpenes, lipids, phlorotannins, fatty acids, and sterols, have been isolated from *Dilophus* species. Diterpenes from members of the genus *Dilophus* generally exhibit potent feeding-deterrent activities, which greatly conducive to their successful survival and reproduction in the highly complex marine environments. Most of the diterpenes from *Dilophus* species share the same structural skeletons with those from *Dictyota* species since they are taxonomically related genera (*Dilophus* and *Dictyota*). Some diterpenes from *Dilophus* species, especially the compounds with the natural cubebane skeleton derivatives, are deemed as the characteristic secondary metabolites of this genus and possess chemotaxonomic significance. Diterpenes from the *Dilophus* species generally exhibit potent biological activities, such as antibacterial and feeding-deterrent activities.

In 2013, linear diterpenes from the marine brown alga *Bifurcaria bifurcata* were reviewed. Diterpenes derived from the brown algae of the genus *Dictyota* were also reviewed in 2018. In the present review, we systematically summarized the structures and bioactivities of diterpenes derived from *Dilophus* species, with more than 60 references cited. Up to the present time, a total of 124 diterpenes have been reported from members of the genus *Dilophus*, most of which are discovered from the marine brown alga *Dilophus spiralis*. Many of these diterpenes have exhibited concerned activities, including antibacterial and feeding-deterrent activities. In order to clarify the structural characteristics of diterpenes derived from *Dilophus* species, they are divided into 4 groups, including groups I to III and others, according to the

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literature on chemotaxonomic study of diterpenes from *Dictyota* species\(^{10,11}\) (Figure 1).

**Diterpenes of Group I**

According to the widely cited literature on chemotaxonomy, group I consists of diterpenes obtained by the first formal cyclization of the geranyl-geraniol precursor between C-1 and C-10.\(^{12}\) Up to present, a total of 41 diterpenes of group I have been purified from *Dilophus* species with diverse skeletons, including secospatane, spatane, prenylated-guaiane, and prenylated-bicyclogermacrone. Among these diterpenes, main compounds are diterpenes with secospatane skeletons. Tables 1 and 2 summarize 41 diterpenes of group I derived from brown algae of the genus *Dilophus* (Figures 2 and 3; Tables 1 and 2).
Secospatane Diterpenes

Up to the present day, a total of 19 secospatane diterpenes have been isolated from Dilophus species, almost half of which are reported from the alga *Dilophus okamurai* (Table 1). Most of the secospatane diterpenes have exhibited feeding-deterrent activity. The chemical structures of compounds 1 to 19 are shown in Figure 2.

A family of secospatane diterpenes, named secospatacetals A to E (1-5), has been isolated from *D. okamurai*, which is collected at Kikizu beach of Ehime Prefecture, Japan.9 Nine secospatane diterpenes (6-14) are isolated from the brown alga *Dilophus marginatus* collected from Collaroy, New South Wales, Australia.8 Compounds 6 and 7 are also obtained from the brown alga *D. okamurai*.17,23 Compound 6 shows an antimicrobial activity against the bacteria *Bacillus subtilis*.23 Compound 6 displays selective feeding-deterrent activity against the young abalone *Haliotis discus hannai* with an electivity index (Ei) value of 0.49.17 Another diterpene, compound 15, is obtained from the brown alga *D. okamurai* collected on the coast of Kamaishi, Iwate Prefecture, Japan.11 Compound 15 also shows moderate feeding-deterrent activity against the young abalone *Haliotis discus hannai*.15,21 Compound 16, a feeding-deterrent diterpene, is isolated from the brown alga *D. okamurai* collected at Karakuwa Peninsula, Japan.25 Two secospatane diterpenes with feeding-deterrent activity, compounds 17 and 18, are obtained from the brown alga *D. okamurai* collected on the coast of Kamaishi, Iwate Prefecture, Japan.11 They are also isolated from the same alga collected from the west coast of Awashima, Niigata Prefecture, Japan.17 Compounds 17 and 18 show strong feeding-deterrent activity against the young abalone *Haliotis discus hannai* with an Ei value of 0.85 and 0.65, respectively.17 Another diterpene, named dilkamural (19), is isolated from the brown alga *D. okamurai* collected from Shikoku Island of Japan. Compound 19 displays an antimicrobial activity against the bacteria *B. subtilis*, a Gram-positive microorganism, showing a clear zone with diameter of 12 mm at 10 µg/disk in the agar-disk diffusion method. Compound 19 also exhibits weak inhibitory activity against a species of plant pathogenic mold (*Colletotrichum lagarum*) and feeding-deterrent activity. Besides, as a chemical defense substance, compound 19 shows feeding-deterrent activity against mollusks and fish.23

Spatane Diterpenes

Up to the present time, 9 spatane diterpenes have been found in *D. marginatus* or *D. okamurai* (Figure 3; Table 2). Five spatane compounds (20-24) are isolated from the brown alga *D. marginatus* collected from Collaroy, New South Wales, Australia.8 Compounds 21 and 22 are also isolated from the brown alga *D. okamurai* collected on the coast of Kamaishi, Iwate Prefecture, Japan.11 Compounds 21 and 22, 2 configurational isomers, inhibit the settlement and metamorphosis of the swimming larvae (veliger) of the abalone *Haliotis discus hannai* Ino.25 Additionally, compound 22 exhibits strong feeding-deterrent activity against the young abalone with an Ei value of 0.66.17,26 Four spatane diterpenes, compounds 25 to 28, are obtained from the brown alga *D. okamurai* collected at Karakuwa Peninsula, Japan.27 Compound 25 is also isolated from the brown alga *D. marginatus* collected from Collaroy, New South Wales, Australia.9 Compound 25 displays feeding-deterrent activities against the young abalone *Haliotis discus hannai* with an Ei value of 0.90.17 Compared with compounds 21 and 22, compound 26 shows stronger

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**Table 1. Bioactivities of Secospatane Diterpenes (1-19) From the Genus Dilophus.**

| Metabolites          | Sources                | Location             | Activities                                      | References |
|----------------------|------------------------|----------------------|------------------------------------------------|------------|
| Secospatacetals      | *Dilophus okamurai*    | Kikizu, Japan        | nd                                              | 22         |
| A-E (1-5)            |                        |                      |                                                 |            |
| 6                    | *Dilophus marginatus*  | Collaroy, Australia  | Antimicrobial activity                          | 8,17,23    |
| 7                    | *Dilophus okamurai*    | Collaroy, Australia  | Selective feeding-deterrent activity            | 8,17       |
| 8-14                 | *Dilophus marginatus*  | Awashima Beach, Japan| nd                                              | 8          |
| 15                   | *Dilophus okamurai*    | Kamaishi Beach, Japan| Moderate feeding-deterrent activity             | 11,24,25   |
| 16                   | *Dilophus okamurai*    | Karakuwa Peninsula, Japan| nd                                                  | 25         |
| 17                   | *Dilophus okamurai*    | Awashima Beach, Japan| Strong feeding-deterrent activity               | 11,17,24   |
| 18                   | *Dilophus okamurai*    | Kamaishi Beach, Japan| Moderate feeding-deterrent activity             | 11,17      |
| 19                   | *Dilophus okamurai*    | Shikoku Island, Japan| Antimicrobial activity                          | 23         |
| Moderate feeding-deterrent activity 11,24,25 |                      |                      | Weak inhibitory activity                        |            |
| Dilkamural (19)      | *Dilophus okamurai*    |                      | Feeding-deterrent activity                      |            |

nd, not determined.
feeding-deterrent properties against the young abalone *Haliotis discus hannai* Ino. 25

**Prenylated-Guaiane Diterpenes**

Up to present, 7 prenylated-guaiane diterpenes with the perhydrolazulene skeleton have been obtained from *Dilophus* species (Figure 3; Table 2).
values of 40.2, 24.6, 27.4, and 37.5 µg/mL, respectively. Compound 30 shows moderate cytotoxicity against 4 different cell lines HepG2, WI-38, VERO, and MCF-7 with IC_{50} values of 39.2, 22.4, 28.3, and 39.2 µg/mL, respectively. Compounds 29 and 30 display potent antithrombotic activity against thrombin with 50% inhibition at 0.68 mM. Compound 29 displays remarkable antifouling activity against the invasive freshwater mussel Limnoperna fortunei at the concentration of 4.7 µg/cm². Moreover, a total synthesis of compound 29 has been accomplished. Two prenylated-guaiane diterpenes, termed dictyols C (31) and E (32), are separated from the alga Dilophus mediterraneus. They are also obtained from the alga Dilophus fasciola. Compound 32 is also isolated from the brown alga Dilophus uncinus, Dilophus ligulatus, and D. spiralis. Compound 31 displays moderate antifouling activity against the freshwater mollusk L. fortunei at the concentration of 9.5 and 12 µg/cm² without any toxic activity. Compound 31 shows weak protective activity against DNA damage and low antioxidant activity for 2,2'-azinobis-(3-ethylbenzothiazoline)-6-sulfonic acid(ABTS) and erythrocytes hemolysis. Compound 32 shows moderate inhibitory activity against rat liver diacyl glycerol acyl transferase with IC_{50} values of 46.0 µM. A prenylated-guiane diterpene, termed dictyoxide (33), is isolated from the brown alga D. ligulatus collected at Acti Castello, Sicily, Italy. Compound 33 is also separated from the alga D. spiralis collected from Elafonissos Island, Greece. Another prenylated-guiane diterpene, termed dictyone (34), is purified from the brown alga D. okamurai collected from the west coast of Awashima, Niigata Prefecture, Japan. Compound 34 displays powerful cytotoxicity against 3 proliferating mouse cell lines, including a normal fibroblast line NIH3T3 and 2 virally transformed forms SSVNIH3T3 and KA31T, with IC_{50} values ranging from 5 to 20 µg/mL. A prenylated-guaiane diterpene, named dictytriene B (35), is obtained from the brown alga D. spiralis collected from Elafonissos Island, Greece.

**Other Diterpenes of Group I**

Four prenylated-bicyclogermacrane diterpenes, compounds (36-39), are separated from the brown alga Dilophus prolificans collected from the New South Wales coast near Sydney, Australia. A prenylated-germacrane diterpene, named dilopolhol (40), is isolated from the brown alga D. ligulatus collected from the littoral zone of the east coast of Sicily (Porto Palo), Italy. Obscuronatin (41) is extracted from the brown alga D. spiralis collected in Greece. In addition, a total synthesis of compound 41 has been achieved. The chemical structures of compounds 20 to 41 are shown in Figure 3.

**Diterpenes of Group II**

According to the literature widely cited, diterpenes of group II include those derived by the first formal cyclization of the geranyl-geraniol precursor between C-1 and C-11. The
diterpene skeletons of group II consist of dolabellane, dolastane, and so on. Up to the present time, a total of 46 diterpenes of group II have been separated from Dilophus species, and almost all of them are dolabellane diterpenes. Table 3 summarizes 46 diterpenes of group II identified from Dilophus species. The chemical structures of compounds 42 to 87 are shown in Figure 4.

**Dolabellane Diterpenes**

Dolabellane natural products have been obtained from a variety of marine organisms, including marine algae, sponges, herbivore sea hare, and terrestrial plants. Dolabellane diterpenes possess a 5,11-carbocyclic skeleton, which is generally substituted by hydroxyl, epoxide, and glucoside functional groups. Dolabellane diterpenes exhibit significant biological activities, such as antiviral, cytotoxic, molluscicidal, and phytotoxic activities. A total of 38 dolabellane diterpenes have been isolated from the genus Dilophus, among which 30 are obtained from the brown alga *D. spiralis* (Figure 4; Table 3).

A series of dolabellane diterpenes, compounds 42 to 71, have been isolated from the brown alga *D. spiralis* collected on Elafonissos Island, Greece. Moreover, compound 58 is also separated from the brown alga *D. okamura* collected from the west coast of Awashima, Niigata Prefecture, Japan. Compounds 42 to 47 exhibit powerful antibacterial activity against the strain of epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA-16), with minimal inhibiting concentration (MIC) values of 16, 16, 16, 8, 4, and 8 µg/mL, respectively. Compound 58 shows strong feed-deterrent activity with an Ei value of 0.93. Compound 59 shows significant antibacterial activity against standard laboratory strain ATCC 25923, strain epidemic MRSA-15 (EMRSA-15), EMRSA-16, macrolide-resistant variant RN4220, multidrug-resistant effluxing strains SA1199B and XU212 with MIC values of 8, 8, 2, 8, 8, and 8 µg/mL, respectively. Compound 60 also exhibits powerful antibacterial activity against ATCC 25923, EMRSA-15, EMRSA-16, RN4220, SA1199B, and XU212 with MIC values of 4, 4, 2, 2, 4, and 4 µg/mL, respectively. Four dolabellane diterpenes, compounds 72 to 75,
are obtained from the brown alga *D. mediterraneus* collected from St. Paul’s Bay, Malta. Three ichthyotoxic diterpenes, compounds 76 to 78, are isolated from the brown alga *D. fasciola* collected near Rovinj, Yugoslavia. In fish toxicity bioassay, compounds 76 to 78 display potent ichthyotoxic activity against *Gambusia patruelis* at a concentration of 50 ppm. In root growth bioassay, compounds 76 to 78 show moderate phytotoxic activity against *Hordeum vulgare* at a concentration of 100 ppm. A dolabellane diterpene, named epoxyoxodolabelladiene (79), is separated from the brown alga *D. ligulatus* collected from the Bay of Villefranche-sur-Mer, France. Compound 79 exhibits moderate cytotoxic activity against KB (human nasopharynx carcinoma), NSCLCN6-L16 (human nonsmall cell lung carcinoma), and P-388 (murine leukemia) cells with ED50 values of 25.39, 16.66 to 16.78, and 6.5 µg/mL, respectively. Compound 79 shows moderate antifungal activity against *Aspergillus fumigatus*, *Microsporum canis*, and *Trichophyton mentagrophytes* with MIC values of 160, 130, and 130 µg/mL, respectively.

Table 3. Bioactivities of Group II Diterpenes (42-87) From the Genus *Dilophus*.

| Structure class | Sources | Metabolites | Sources/location | Activities | References |
|----------------|---------|-------------|-----------------|------------|------------|
| Dolabellane     | *Dilophus spiralis* | 42-47 | Elafonissos Island, Greece | Moderate antibacterial activity | 19 |
|                 |         | 48-57 | Elafonissos Island, Greece | nd | 19 |
|                 |         | 58 | Elafonissos Island, Greece | Strong feed-deterrent activity | 19 |
|                 |         | 59-60 | Elafonissos Island, Greece | Significant antibacterial activity | 44 |
|                 | *Dilophus okamurai* | 61-71 | Elafonissos Island, Greece | nd | 44 |
|                 |         | 58 | Awashima Beach, Japan | Strong feed-deterrent activity | 17 |
| Dolastane       | *Dilophus spiralis* | 72-75 | St. Paul’s Bay, Malta | nd | 33 |
|                 |         | 76-78 | Rovinj, Yugoslavia | Ichthyotoxic activity | 45 |
|                 |         |     | | Phytophagic activity | 45 |
|                 | *Dilophus ligulatus* | Epoxyoxodolabelladiene (79) | Villefranche-sur-Mer, France | Cytotoxic activity | 46 |
|                 |         |     | | Weak antifungal activity | 46 |
| Dolastane       | *Dilophus spiralis* | 80-81 | Elafonissos Island, Greece | Moderately cytotoxic | 47 |
|                 |         | 82-84 | Elafonissos Island, Greece | nd | 47 |
|                 |         | 85-87 | Elafonissos Island, Greece | nd | 28 |

nd, not determined.

Diterpenes of Group III

According to the widely cited literature on chemotaxonomy, group III includes diterpenes obtained by the first formal cyclization of the geranyl-geraniol precursor between C-2 and C-10. The diterpene skeletons of group III include xenicane, cycloxeniane, crenulidane, and crenulane. Up to the present day, 23 diterpenes of group III have been separated from *Dilophus* species. Major diterpenes of group III from species of *Dilophus* are xenicane-type diterpenes functionalized with oxidation, epoxidation, and condensation to form monocyclic, bicyclic, and tricyclic structures. Tables 4 and 5 summarize 23 diterpenes of group III identified from *Dilophus* species. (Figures 5 and 6; Tables 4 and 5).

Xenicane Diterpenes

Xenicane diterpenes, possessing cyclooctane skeleton with as a common structural feature, are a large class of marine diterpenes. Up to the present time, 10 xenicane diterpenes have been separated from members of the genus *Dilophus* (Table 4). The chemical structures of compounds 88 to 97 are shown in Figure 5.
A series of xenicane diterpenes, including acetyldictyolal (88), dictyotalide B (89), neo-dictyolactone (90), and dictyolactone (91) and (92), are purified from the brown alga *D. ligulatus* collected from the Bay of Villefranche-sur-Mer, France. Both compounds 88 and 89 are also separated from the brown algae *D. fasciola* and *D. spiralis*, respectively. Compound 91 is also extracted from the brown alga *D. okamurai* collected from the west coast of Awashima, Niigata Prefecture, Japan. Compound 88 exhibits significant cytotoxic activity against P-388, KB, and NSCLC-N6-L16 cells with ED₅₀ values of 1.50 to 1.66, 9.1, and 5.55 to 5.80 μg/mL, respectively. Compound 88 shows weak antifungal activity against *A. fumigatus*, *M. canis*, and *T. mentagrophytes*. Compound 89 displays moderate cytotoxic activity against P-388, KB, and NSCLC N6-L16 with ED₅₀ values of 16.6 to 19.56, 26.43, and 21.22 μg/mL, respectively. Compounds 90 to 92 show strong cytotoxic activity against P-388, P388/DOX (murine leukemia expressing the multidrug-resistance gene, MDR), KB, and NSCLC N6-L16 cells. Compound 91 also exhibits strong feed-deterrent activity with an EI value of 0.74. A cytotoxic diterpene, named fukurinolal (93), is isolated from the brown alga *D.*
ligulatus and D. okamurai, respectively.\textsuperscript{9,34} Compound 93 exhibits significant cytotoxic activity against KB, P-388, P388/DOX, and NSCLC-N6 cells with \textit{ED}_{50} values of 2.1, 3.9, 9.3, and 10 µg/mL, respectively.\textsuperscript{9} Two antibacterial diterpenes, termed dictyodial (94) and isodictyohemiacetal (95), are obtained from the brown alga \textit{D. mediterraneus} collected from St. Paul’s Bay, Malta.\textsuperscript{33} Compound 94 shows potent antibacterial activity against \textit{Staphylococcus aureus} and \textit{B. subtilis} as well as antifungal activity against \textit{Candida albicans}.\textsuperscript{55} Moreover, a total synthesis of compound 94 has been accomplished.\textsuperscript{56} Two xenicane diterpenes, termed dilophic acid (96) and compound (97), have been separated from the brown alga \textit{D. guineensis} collected from Vega Baja, Puerto Rico. Compound 96 shows slight Gram-positive antimicrobial activity and weak ichthyotoxic activity against goldfish \textit{Carassius auratus} at a dose of 50 µg/mL.\textsuperscript{35}

### Cycloxeniane Diterpenes

Cycloxeniane-type diterpenes possessing 2,6-cyclo-xenicane skeleton are rare diterpenes from marine organisms.\textsuperscript{34} Up to the present time, 7 cycloxeniane diterpenes have been found from \textit{Dilophus} species\textsuperscript{34} (Figure 6; Table 5). A series of cycloxeniane diterpenes (98-103) have been isolated from the alga \textit{D. fasciola} collected in Tunisia.\textsuperscript{34} Compound 104 is obtained from the alga \textit{D. spiralis} collected in Greece.\textsuperscript{34}

### Crenulidane Diterpenes

Crenulidane diterpenes bearing the bicyclo nonane skeleton exhibit diverse activities, including antimicrobial, cytotoxic, and antifungal activities.\textsuperscript{39,46} Up to the present, 4 crenulidine

### Table 4. Bioactivities of Xenicane Diterpenes (88-97) From the Genus \textit{Dilophus}.

| Metabolites       | Sources                              | Activities                                      | References |
|-------------------|--------------------------------------|-------------------------------------------------|------------|
| Acetyldictyolal (88) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Significant cytotoxic activity                    | 34,46      |
|                   | \textit{Dilophus spiralis}, Greece    | Weak antifungal activity                         |            |
|                   | \textit{Dilophus fasciola}, Greece    |                                                  |            |
| Dictyotalide B (89) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Moderate cytotoxic activity                      | 9,46       |
| Neodictyolactone (90) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Strong cytotoxic activity                        | 34,46      |
| Dictyolactone (91) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Strong cytotoxic activity                        | 17,46      |
|                   | \textit{Dilophus okamurai}, Awashima Beach, Japan | Strong feed-deterrent activity                    | 46         |
| Fukurinolal (93)   | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Significant cytotoxic activity                    | 9,54       |
|                   | \textit{Dilophus okamurai}            |                                                  |            |
| Dictyodial (94)    | \textit{Dilophus mediterraneus}, St. Paul’s Bay, Malta | Potent antibacterial activity                     | 33,35,56   |
| Isodictyohemiacetal (95) | \textit{Dilophus mediterraneus}, St. Paul’s Bay, Malta | Strong cytotoxic activity                        |            |
| Dilophic acid (96) | \textit{Dilophus guineensis}, Vega Baja, Puerto Rico | Slight Gram-positive antimicrobial activity       |            |
|                   |                                       | Weakly ichthyotoxic.                             | 35         |
| 97                | \textit{Dilophus guineensis}, Vega Baja, Puerto Rico | nd                                              | 35         |

nd, not determined.

### Table 5. Bioactivities of Cycloxeniane, Crenulidane, and Crenulane Diterpenes (98-110) From the Genus \textit{Dilophus}.

| Structure class | Metabolites       | Sources                              | Activities                                      | References |
|-----------------|-------------------|--------------------------------------|-------------------------------------------------|------------|
| Cycloxeniane    | 98-103            | \textit{Dilophus fasciola}, Tunisia   | nd                                              | 34         |
|                 | 104               | \textit{Dilophus spiralis}, Greece    | nd                                              | 34         |
| Crenulidane     | Crenuladial (105)  | \textit{Dilophus ligulatus}, Sicily, Porto palo, Italy | Antimicrobial activity                           | 39         |
|                 | Pachylactone (106) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Significant cytotoxicity                         | 34,46,57   |
|                 |                   | \textit{Dilophus spiralis}, Greece    | Weaker antifungal activity                       |            |
|                 | Isoacetoxycrenulatin (107) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Cytotoxicity                                     | 46         |
|                 |                   | \textit{Dilophus spiralis}, Greece    | Weaker antifungal activity                       |            |
| Crenulane       | Acetoxycrenelide (108) | \textit{Dilophus ligulatus}, Villefranche-sur-mer, France | Weak cytotoxicity                               | 9,58       |
|                 | Fukurinolal (109)  | \textit{Dilophus okamurai}             | nd                                              | 54         |
|                 | Sanadaol (110)     | \textit{Dilophus mediterraneus}, St. Paul’s Bay, Malta | Strong algicidal activity                       | 33,34,59,60|
|                 |                   | \textit{Dilophus fasciola}, Tunisia   |                                                  |            |

nd, not determined.
Diterpenes have been isolated from the genus *Dilophus* (Figure 6; Table 5).

Four crenulane diterpenes, named crenuladial (105), pachy-lactone (106), isoacetoxycrenulatin (107), and acetoxycrenulide (108), have been purified from the brown alga *D. ligulatus*.9,39,46 Compound 106 is also separated from the brown alga *D. spiralis* collected in Greece.34 Compound 105 exhibits moderate antimicrobial activity against *S. aureus* and *Micrococcus luteus* with MIC values of 75 and 75 µg/mL, respectively.99 Compound 106 shows significant cytotoxic activity against P-388, P388/DOX, KB, and NSCLC-N6-L16 cells with MIC values of 4.8, 7.9, 5.2, and 1.6 µg/mL, respectively.46 Compounds 106 and 107 exhibit weak antifungal activity against *A. fumigatus*, *M. canis*, and *T. mentagrophytes*.46 Compound 108 shows weak cytotoxic activity against KB, P-388, P388/DOX, and NSCLC-N6 cells.9 In addition, total synthesis of compounds 106 and 108 has been accomplished.57,58

**Crenulane Diterpenes**

A crenulane diterpene, termed fukurinal (109), has been isolated from the brown alga *D. okamurai*.54 Another crenulane
diterpene, named sanadaol (110), is obtained from the brown alga D. mediterraneus collected from St. Paul’s Bay, Malta.\textsuperscript{33} Compound 110 is also separated from the alga D. fasciola collected in Tunisia.\textsuperscript{34} This compound exhibits strong (>95\%) algicidal activity against the red-tide phytoplankton Heterosigma akashiwo and Karenia mikimotoi at a dose of 10 to 20 μg/mL.\textsuperscript{59} Moreover, a total synthesis of compound 110 has been accomplished.\textsuperscript{60} The chemical structures of compounds 98 to 110 are shown in Figure 6.

### Others

Except for the above-mentioned diterpenes of groups I to III, some diterpenes have been discovered from members of the genus Dilophus. Up to the present day, a total of 14 diterpenes with new skeleton have been separated from Dilophus species, most of which are cubebane diterpenes. Table 6 summarizes 14 other diterpenes identified from Dilophus species. The chemical structures of compounds 111 to 124 are shown in Figure 7.
Cubebe Diterpenes

Cubebe-type diterpenes possessing unprecedented [5,3,6] tricyclic ring skeleton generally exhibit feeding-deterrent properties. A feeding-deterrent cubebe diterpene, compound 111, is isolated from the brown alga D. okamurai. Compound 111 exhibits weak feeding-deterrent activity against the young abalone Haliotis discus hannai. Three cubebe diterpenes, compounds 112 to 114, are obtained from the brown alga D. okamurai collected on the coast of Kamaishi, Iwate Prefecture, Japan. Compound 112 displays weak feeding-deterrent activity against the young abalone Haliotis discus hannai. Compounds 113 and 114 show moderate feeding-deterrent activity. Three cubebe-type diterpenes, compounds 115 to 117, are obtained from the brown alga D. marginatus collected from Collaroy, New South Wales, Australia. The stereochemistry of compounds 115 to 117 cannot be determined due to the limitation of analytical techniques (Figure 7; Table 6).

Other Diterpenes

Two cytotoxic diterpenes possessing a cyclobutenone moiety [4,5], named acetylnorhociarenone (118) and isooacetylnorhociarenone (119), have been isolated from the brown alga D. ligulatus collected from the Bay of Villefranche-sur-Mer, France. Compound 118 exhibits powerful cytotoxic activity against P-388 and NSCLC-N6 cells with ED_{50} values of 4.4 and 5.4 µg/mL, respectively. Compound 119 shows cytotoxic activity against P-388 and NSCLC-N6 cells with ED_{50} values of 6 and 6.82 µg/mL, respectively. Two rare diterpenes, named dilospiranes A (120) and B (121), are isolated from the brown alga D. spiralis collected from the coast of Elafonissos Island, Greece. Compounds 120 and 121 have no significant inhibitory effect on the regulation of hypoxia-inducible factor-1. Compound 121 exhibits in vitro antitumor activity against the human glioblastoma cell line (HS683), PC-3, MCF-7, glioma (U373), A549, and melanoma cell lines (SKMEL-28) with ED_{50} values of 68 ± 1, 58 ± 7, 67 ± 1, 70 ± 1, 66 ± 2, and 65 ± 2 µg/mL, respectively. Dicyterpenoids A and B (122 and 123) are obtained from the brown alga D. okamurai collected from the west coast of Awashima, Niigata Prefecture, Japan. Compounds 122 and 123 exhibit selective feeding-deterrent activity against the young abalone Haliotis discus hannai with Ei values of 0.59 and 0.23, respectively. A rare diterpene, named fasciola-7,18-dien-17-al (124), is isolated from the brown alga D. fasciola collected from the beach of Portopalo, Italy (Figure 7; Table 6).

Conclusion

The genus Dilophus is a rich source of various natural products with novel pharmacological and biological activities. Significant progress has been made in the discovery of biologically active secondary metabolites from this genus. More than 200 new natural compounds have been isolated from this genus at the present time, most of which are diterpene compounds (124 compounds). More than half of these diterpenes belong to groups I and II (41 and 46 compounds, respectively). A total of 124 diterpenes of 17 skeletal classes have been reported and are distributed as follows: group I (41 diterpenes of 5 skeletal classes), group II (46, 2), group III (23, 4), and others (14, 6). The alga D. spiralis has been proved to be an important producer of diterpenes since 50 structurally diverse diterpenes, including 30 dolabellane diterpenes and 8 dolastane diterpenes, have been isolated from this species. It appears that D. spiralis is the most representative species of the genus. Secospatane diterpenes are mainly found in 3 species, D. okamurai, D. marginatus, and D. spiralis. Most of these diterpenes from Dilophus species exhibit strong feeding-deterrent activity. The fact proved that diterpenes from Dilophus species may play a central role in survival of marine organisms in the complex marine environment. Moreover, 14 compounds with novel skeletons, compounds 111 to 124, have been separated from Dilophus species, exhibiting the genus-genus biosynthetic diversity between 2 genera Dilophus and Dictyota.

However, there are some problems for further drug discovery from the genus Dilophus, including the development of new technologies for the collection of more algae of this genus, multitarget screening assays, isolation of minor components, and total synthesis. First, over the past decade, only 48 diterpenes have been isolated from Dilophus species. Moreover, most diterpenes from this genus are derived from the algae collected from the coastal areas of Japan, Greece, and Australia. It is necessary to collect more algae of this genus from different countries and regions. Combination of related disciplines and technologies, including multitarget screening assay, isolation of minor components, and bioassay-directed separation with liquid chromatography-mass spectrometry (LC/MS)-based analysis methods, would greatly promote the discovery of more bioactive diterpenes from the genus Dilophus in further studies. Second, the total syntheses of 6 compounds, including compounds 29, 41, 94, 106, 108, and 110, have been successfully achieved. More efforts should be devoted to promote the total synthesis of the active diterpenes from the genus Dilophus. Successful total synthesis will benefit structural optimization of natural diterpenes for further bioactivity assessment, as well as for pharmacological and clinical applications. Third, various biological activity assays should be developed, including multitarget screening assays, virtual screening, in vivo animal studies, and in vitro experiments, to promote the discovery of new promising lead drugs.

In the present review, we summarized the diterpenes derived from members of the genus Dilophus at the present time, and our study provided valuable insights into new diterpenes from the genus Dilophus.

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