




Review

# Natural Product Chemistry of Gorgonian Corals of Genus *Junceella*—Part III

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**Abstract:** The structures, names, bioactivities, and references of 82 natural products, including 48 new metabolites, purified from the gorgonian corals belonging to the genus *Junceella* are described in this review. All compounds mentioned in this review were obtained from *Junceella fragilis*, *Junceella gemmacea*, *Junceella juncea*, and *Junceella* sp., collected from tropical Indo-Pacific Ocean. Some of these compounds exhibited potential biomedical activities.

**Keywords:** *Junceella*; gorgonian; briarane; biomedical activity

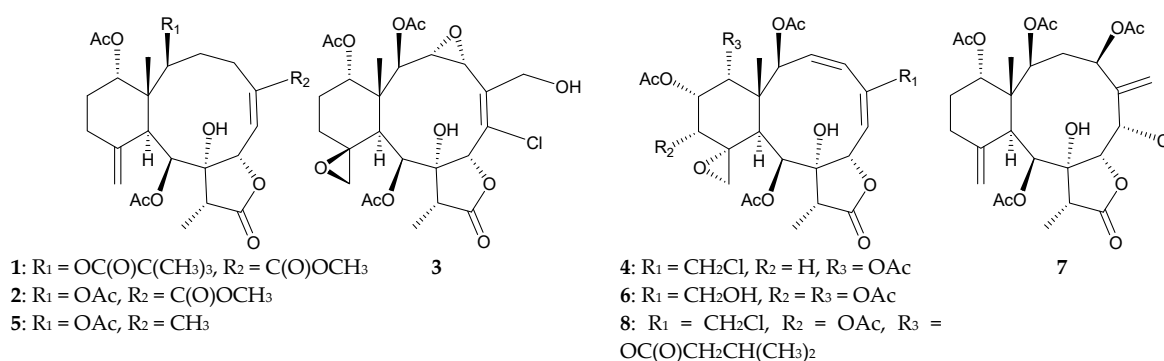
## 1. Introduction

Following previous review articles focused on marine-origin natural products, this review covers the literature from October 2011 to August 2018, and describes 82 natural products (including 48 new metabolites) from gorgonian corals belonging to the genus *Junceella* (family Ellisellidae) [1–4]. Extending from previous reviews in 2004 and 2011 [5,6], this review provides structures, names, bioactivities, and references for all compounds including briarane- and norcembrane-type diterpenoids, sterol, and nucleosides. Many of these compounds exhibited interesting bioactivities in vitro, which might indicate a potential for use in biomedical applications. This survey of natural products from *Junceella* is presented taxonomically according to species.

## 2. Junceella

### 2.1. *Junceella Fragilis*

Eight 8-hydroxybriaranes, including four new compounds, frajunolides P–S (1–4), and four known metabolites, umbraculolide A (5) [7,8], juncenolide C (6) [9], junceallonoid A (7) [10], and juncin R (8) [11], were isolated from *J. fragilis*, collected from the waters of Taiwan [12] (Figure 1). The structures of briaranes 1–4 were established by spectroscopic methods, and determination of the absolute configuration of 1 was completed by X-ray diffraction analysis [12]. At a concentration of 10 µg/mL, briaranes 1 and 2 were found to exert inhibitory activities on elastase release (inhibition rate = 35.6% and 34.1%, respectively) and superoxide anion production (inhibition rate = 32.5 and 28.7%, respectively) by human neutrophils [12].



**Figure 1.** Structures of frajunolides P–S (1–4), umbraculolide A (5), juncenolide C (6), junceallonoid A (7), and juncin R (8).

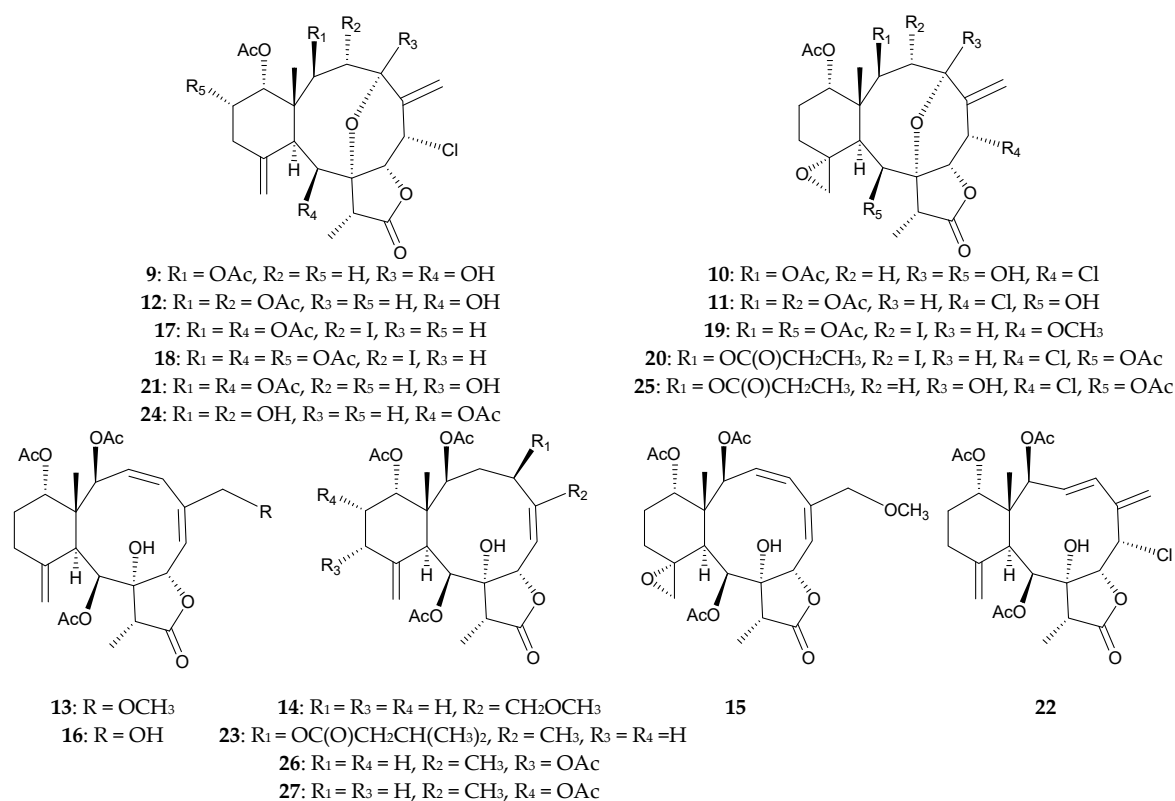
In 2014, *J. fragilis*, collected from the South China Sea, was found to contain 12 new briaranes, fragilisins A–L (9–20) [13], along with seven known analogues, junceallolides A (21) and B (22) [14], junceol A (23) [15], junceallonoid D (24) [16,17], fragilide C (25) [18], and frajunolides A (26) [19] and E (27) [20] (Figure 2) [13]. The structures of briaranes 9–20 were determined by spectroscopic methods. Briaranes 17–20 were the first iodine-containing briaranes to be isolated. The absolute configuration of briarane 9 was confirmed by single-crystal X-ray diffraction data [13]. Briaranes 13, 14, 18, 21, and 24 showed potent antifouling activities against the settlement of barnacle *Balanus amphitrite* larvae, with EC<sub>50</sub> values of 14.0, 12.6, 11.9, 5.6, and 10.0 µM, respectively [13].

In addition, a new norditerpenoid, fragilolide A (28), 16 new briaranes, fragilolides B–Q (29–44), along with two known briaranes, frajunolides H (45) [20] and N (46) [21], and three known norcembranoids, scabrolide D (47) [22], sinuleptolide (48) [23], and 5-*epi*-sinuleptolide (49) [24–26], were obtained from *J. fragilis*, collected from the inner coral reef around in Hainan Island of China [27] (Figure 3). The structures of metabolites 28–44 were determined by spectroscopic methods, including calculated electronic circular dichroism (ECD) data. The structures, including the absolute configurations of briaranes 37 and 46, were further established by single-crystal X-ray diffraction

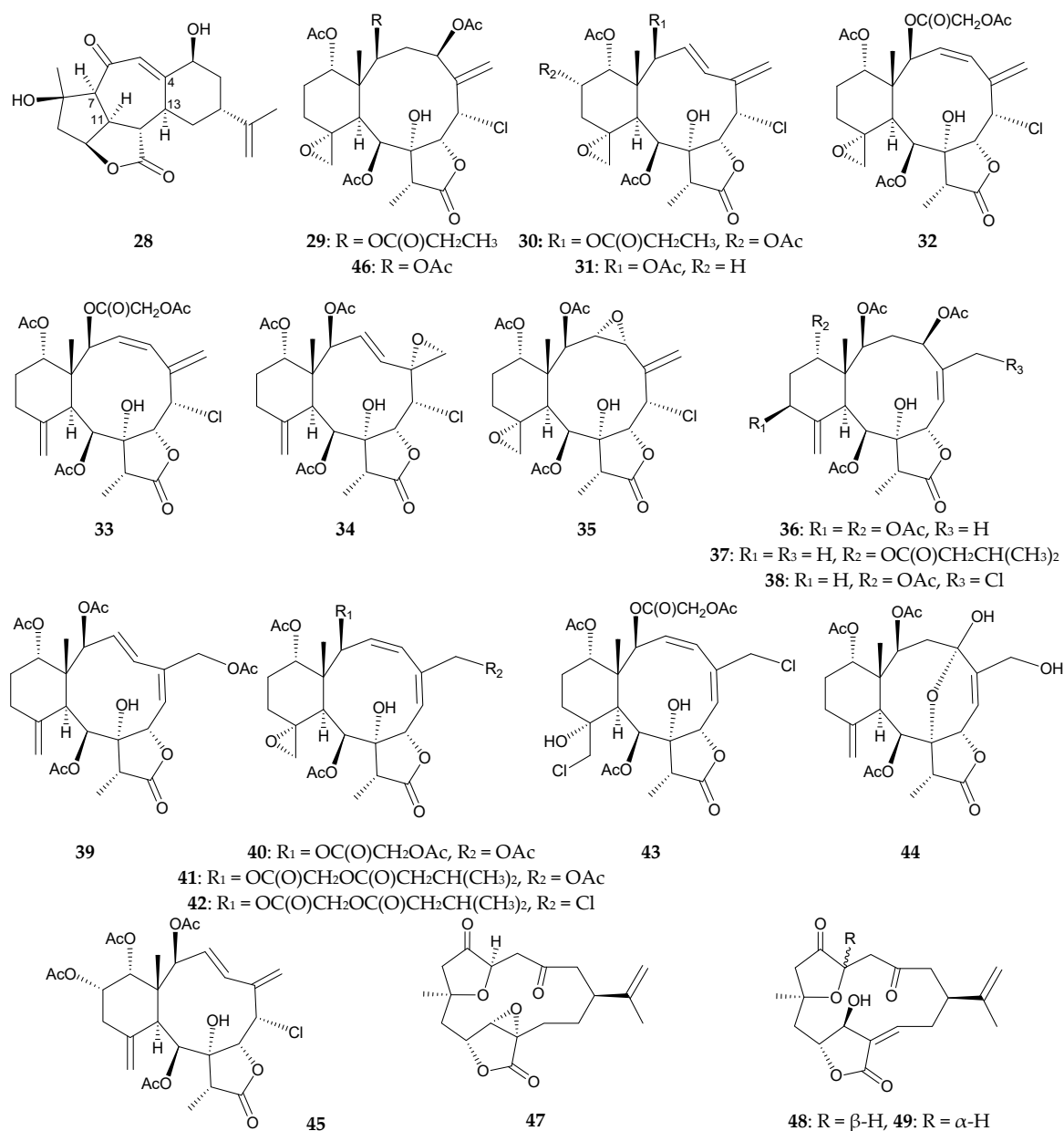
analysis using Flack parameter in this study [27]. Compound **28** featured an unprecedented 4,13- and 7,11-fused tetracyclic norcembranoid [27].

Briarane **45** exhibited cytotoxicity toward Hep G2 (human hepatocellular carcinoma), Huh7 (human hepatocellular carcinoma), SMMC-7721 (human papillomavirus-related endocervical adenocarcinoma), A2780 (human ovarian carcinoma), BGC-823 (human gastric adenocarcinoma), HGC-27 (human gastric carcinoma), MGC-803 (human gastric carcinoma), NCI-H1650 (human bronchoalveolar carcinoma), and PA-1 (human ovarian mixed germ cell tumor) cells with IC<sub>50</sub> values 0.89, 16.52, 0.61, 1.18, 2.10, 0.61, 1.97, 6.47, and 0.42 μM, respectively. Briaranes **31**, **34**, **36**, **39**, **43**, and **46** exerted selective inhibitory effects toward hepatitis B and antigen (HBeAg) in a dose of 10 μM, whereas no activity was observed against the expression of hepatitis B surface antigen (HBsAg) [27].

Moreover, the norcembranoids **28** and **47–49** were assayed for their potential inhibitory effects against nitric oxide (NO) production induced by lipopolysaccharides (LPS) (large molecules consisting of lipids and polysaccharide composed of O-antigen joined by chemical bonds), in RAW264.7 cells, and these four compounds exhibited the inhibitory activities with 27.8%, 43.5%, 56.0%, and 57.9% inhibition, respectively, at a dose of 100 μM [27]. In order to explore the mechanism of these NO inhibitors, the expression of the antioxidant response element (ARE) mediated luciferase and NF-κB was evaluated. Norcembranoids **48** and **49** showed the effects against NF-κB by the inhibitory rates of 25.1% and 28.6% in a dose of 50 μM, respectively. Significant induction of luciferase was observed as the dose of 50 μM for **48** and **49** with 3.8 and 5.6 folds more than that of blank control [27]. The antioxidant capacity of **28** and **47–49** were evaluated by the modified 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) radical cation decolorization assay [27].



**Figure 2.** Structures of fragilisins A–L (**9–20**), juncellolides A (**21**) and B (**22**), juncel A (**23**), juncellonoid D (**24**), fragilide C (**25**), and frajunolides A (**26**) and E (**27**).



**Figure 3.** Structures of fragilolides A–Q (28–44), frajunolides H (45) and N (46), scabrolide D (47), sinuleptolide (48), and 5-*epi*-sinuleptolide (49).

In 2017, Cheng et al. reported the occurrence of four pairs of chlorinated briarane derivatives, including five new metabolites, 3-deacetylpraelolide (50), 13- $\alpha$ -acetoxy-3-deacetylpraelolide (51), 13- $\alpha$ -acetoxy-2-deacetylpraelolide (52), 13- $\alpha$ -acetoxy-3-deacetyljunceellin (53), 13- $\alpha$ -acetoxy-2-deacetyljunceellin (54), along with three known metabolites, fragilide J (55) [28], 3-deacetyljunceellin (56), and 2-deacetyljunceellin (57) [29], from *J. fragilis*, collected off the inner coral reef in Hainan Island, China (Figure 4), although briaranes 56 and 57 were obtained as a pair of inseparable mixture [30].

The structures of briaranes 50–54 were elucidated by spectroscopic methods in association with chemical conversion. The absolute configurations of briaranes 50 and 55 were further determined by acetylation of these two compounds to yield the same crystal product and analyses of X-ray crystal data of this compound by *Flack* parameter further confirmed the absolute configurations of briaranes 50 and 55 [30], although briaranes 56 and 57 existed in an inseparable mixture in CHCl<sub>3</sub> at room temperature. Lowering the temperature to 4 °C resulted in the generation of a crystal, while the

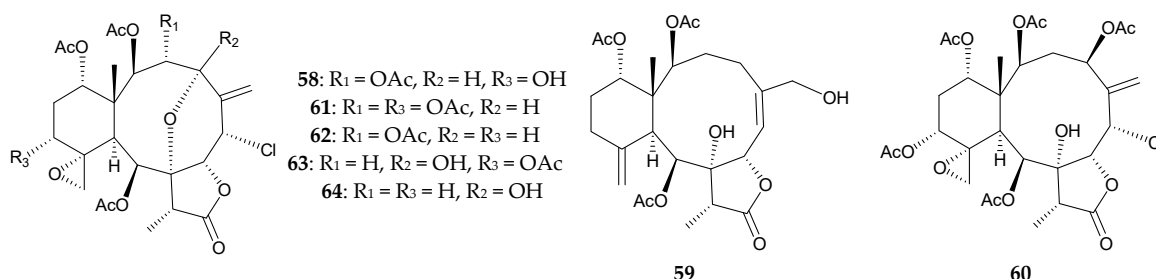
X-ray diffraction analysis using *Flack* parameter determined the crystal product to be in accordance with briarane **56**. Each pair of the isomers (**50/55**, **51/52**, **53/54**, and **56/57**) featured by dynamical interconversion through as acetyl migration in 1,2-diol, which was postulated to be generated under the formation of cyclic orthoacetate intermediated. In the mixture of briaranes **56** and **57**, increasing temperature gradients resulted in the variation of **56/57** ratio, while the ratio of **56/57** varied from 1:1 to 2:3 at 50 °C [30]. The mixtures of **50/55**, **51/52**, **53/54**, and **56/57** were tested for their inhibitory effects against NO production induced by LPS in RAW264.7 cells and these four components displayed inhibitory activities against NO production with the inhibition rates of 39.4%, 46.4%, 42.7%, and 36.3%, respectively, at a concentration of 50  $\mu$ M [30].



**50:** R<sub>1</sub> = OAc, R<sub>2</sub> = OH, R<sub>3</sub> = H, **55:** R<sub>1</sub> = OH, R<sub>2</sub> = OAc, R<sub>3</sub> = H      **53:** R<sub>1</sub> = R<sub>3</sub> = OAc, R<sub>2</sub> = OH, **54:** R<sub>1</sub> = OH, R<sub>2</sub> = R<sub>3</sub> = OAc  
**51:** R<sub>1</sub> = R<sub>3</sub> = OAc, R<sub>2</sub> = OH, **52:** R<sub>1</sub> = OH, R<sub>2</sub> = R<sub>3</sub> = OAc      **56:** R<sub>1</sub> = OAc, R<sub>2</sub> = OH, R<sub>3</sub> = H, **57:** R<sub>1</sub> = OH, R<sub>2</sub> = OAc, R<sub>3</sub> = H

**Figure 4.** Structures of 3-deacetylpraelolide (**50**), 13- $\alpha$ -acetoxy-3-deacetylpraelolide (**51**), 13- $\alpha$ -acetoxy-2-deacetylpraelolide (**52**), 13- $\alpha$ -acetoxy-3-deacetyljunceellin (**53**), 13- $\alpha$ -acetoxy-2-deacetyljunceellin (**54**), fragilide J (**55**), 3-deacetyljunceellin (**56**), and 2-deacetyljunceellin (**57**).

Two new briaranes, fragilides K (**58**) and L (**59**), along with five known chlorinated briaranes, gemmacolides V (**60**) and X (**61**) [31], praelolide (**62**) [7,14,16,32–37], and juncins P (**63**) [35] and ZI (**64**) [11], were obtained from a Formosan *J. fragilis* [38] (Figure 5).



**58:** R<sub>1</sub> = OAc, R<sub>2</sub> = H, R<sub>3</sub> = OH  
**61:** R<sub>1</sub> = R<sub>3</sub> = OAc, R<sub>2</sub> = H  
**62:** R<sub>1</sub> = OAc, R<sub>2</sub> = R<sub>3</sub> = H  
**63:** R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = OAc  
**64:** R<sub>1</sub> = R<sub>3</sub> = H, R<sub>2</sub> = OH

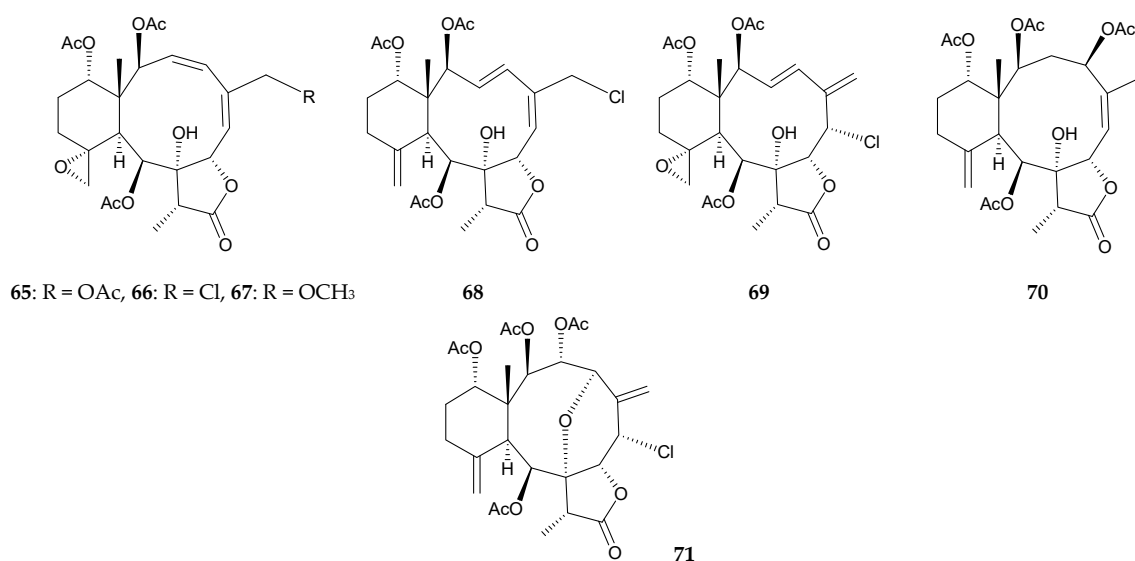
**Figure 5.** Structures of fragilides K (**58**) and L (**59**), gemmacolides V (**60**) and X (**61**), praelolide (**62**), juncins P (**63**) and ZI (**64**).

Based on spectroscopic methods, the structures of briaranes **58** and **59** were elucidated and the cyclohexane rings in **58** and **59** were found to exist in chair and twist boat conformation, respectively. At a concentration of 10  $\mu$ M, briaranes **59**, **61**, and **64** showed anti-inflammatory activity against the expression of pro-inflammatory protein inducible nitric oxide synthase (iNOS) to 49.13%, 36.22%, and 43.33%, respectively, and briaranes **60** and **61** elicited reduction of the pro-inflammatory protein cyclooxygenase-2 (COX-2) to 47.49% and 43.64%, respectively [38].

## 2.2. *Junceella Gemmacea*

Four new briaranes, junceollolides M–P (**65–68**), along with seven known briaranes, junceollolides A–D (**21,22,69,70**) [14] (the structures of briaranes **21** and **22**, please see Figure 2), junceellin A (= junceellin) (**71**) [7,14,16,34–37,39,40], praelolide (**62**) [7,14,16,32–37], and juncin ZI (**64**) [11] (the structures of briaranes **62** and **64**, please see Figure 5) were isolated from *J. gemmacea*, collected from the South China Sea [41] (Figure 6). The structures, including the absolute configurations,

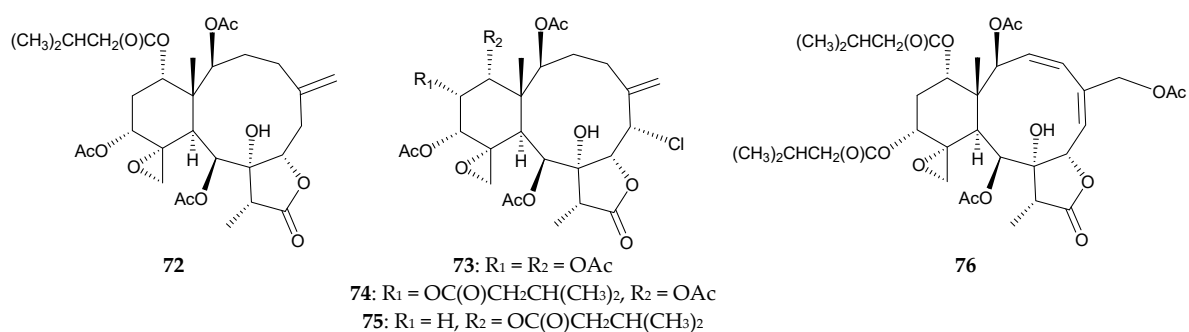
of new briaranes **65–68** were deduced on the basis of spectroscopic analyses, particularly with ECD experiments.



**Figure 6.** Structures of junceollolides M–P (**65–68**), junceollolides C (**69**) and D (**70**), and junceellin A (**71**).

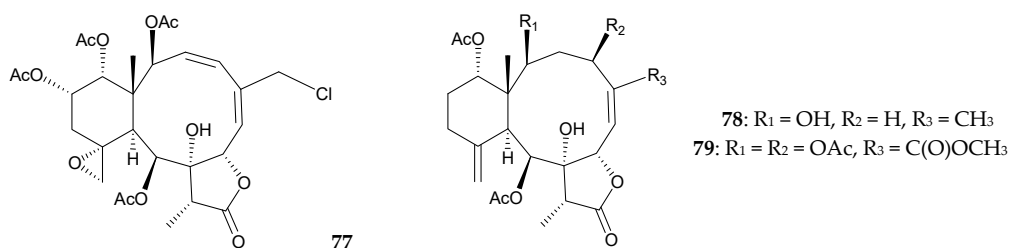
### 2.3. *Junceella Juncea*

Five 8-hydroxybriaranes, including a new briarane, (1*S*\*,2*S*\*,8*S*\*,9*S*\*,10*S*\*,11*R*\*,12*R*\*,14*S*\*,17*R*\*)-11,20-epoxy-14-(3-methylbutanoyl)-2,9,12-triacetoxy-8-hydroxybriar-5(16)-en-18,7-olide (**72**) along with four known metabolites, gemmacolides A (**73**) and B (**74**) [42,43], and juncins H (**75**) [44] and K (**76**) [45], were isolated from *J. juncea* collected from Tuticorin coast of the Indian Ocean (Figure 7) [46]. The structure of briarane **72** was established by spectroscopic data and **72** was found to exhibit activities against the fungi *Aspergillus niger*, *Candida albicans*, and *Penicillium notatum*. Briaranes **73** and **74** displayed activities against the bacteria *Bacillus pumilis* and *Escherichia coli*. While the briaranes **75** and **76** showed activities against *B. subtilis*, *B. pumilis*, *Proteus vulgaris*, and *E. coli* [46].



**Figure 7.** Structures of (1*S*\*,2*S*\*,8*S*\*,9*S*\*,10*S*\*,11*R*\*,12*R*\*,14*S*\*,17*R*\*)-11,20-epoxy-14-(3-methylbutanoyl)-2,9,12-triacetoxy-8-hydroxybriar-5(16)-en-18,7-olide (**72**), gemmacolides A (**73**) and B (**74**), and juncins H (**75**) and K (**76**).

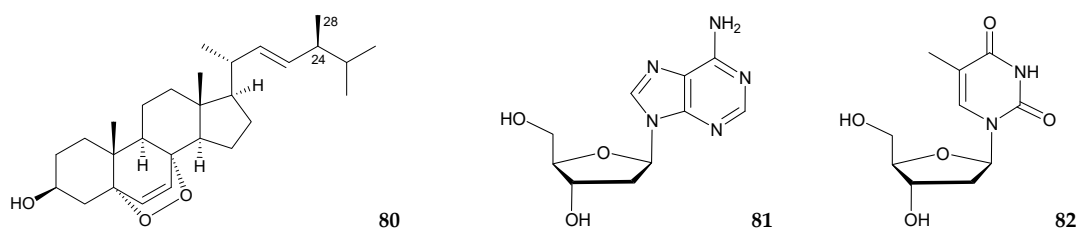
Furthermore, Chang et al. isolated three new briaranes, juncenlides M–O (**77–79**), from *J. juncea*, collected in the waters of Taiwan [47] (Figure 8). Structures of new briaranes **77–79** were established by spectroscopic methods. Briaranes **78** and **79** showed inhibitory activities against the release of elastase and **79** also exhibited inhibitory activity against the generation of superoxide anion [47].



**Figure 8.** Structures of juncenolides M–O (77–79).

#### 2.4. *Junceella* sp.

Three known briaranes, juncellolide A (**21**) [14], praelolide (**62**) [7,14,16,32–37], and juncellin A (**71**) [7,14,16,34–37,39,40], (the structures of briaranes **21**, **62**, and **71**, please see Figure 2, Figure 5, and Figure 6, respectively), and a known sterol, 5 $\alpha$ ,8 $\alpha$ -epidioxy-24( $\xi$ )-methylcholesta-6,22-dien-3 $\beta$ -ol (**80**) [48] (Figure 9), were obtained from the ethanol extract of a gorgonian coral identified as *Junceella* sp., collected off the Vietnam Thu Island in May 2010 [49]. However, by assuming that enantiomeric series for sterols, the configuration at C-24 in **80** should be assigned as *S*\*-form on the basis of the <sup>13</sup>C NMR chemical shift of C-24 and C-28 [50]. Furthermore, two nucleosides, deoxyadenosine (**81**) and deoxythymidine (**82**) [51,52], were obtained from aqueous solution of this specimen. Structures of all isolates were established using spectroscopic data (Figure 9) [49].



**Figure 9.** Structures of 5 $\alpha$ ,8 $\alpha$ -epidioxy-24( $\xi$ )-methylcholesta-6,22-dien-3 $\beta$ -ol (**80**), deoxyadenosine (**81**), and deoxythymidine (**82**).

In the cytotoxic activity test, briaranes **71** and sterol **80** exhibited weak cytotoxicity toward the THP-1 (human acute monocytic leukemia) tumor cells with IC<sub>50</sub> values 55.4 and 130  $\mu$ M, respectively. Sterol **80** also possessed weak clonogenic activity with INCC<sub>50</sub> 53.3  $\mu$ M toward THP-1. Moreover, sterol **80** produced an inhibition zone 12 mm in diameter against *Bacillus subtilis*. Briarane **62** inhibited weakly *Candida albicans*. Briaranes **21** and **71** and sterol **80** inhibited weakly *Vibrio parahaemolyticus* [49].

### 3. Conclusions

The natural products obtained from gorgonian corals belonging to the genus *Junceella* compiled in this review indicated that the terpenoid derivatives, particularly briarane-type diterpenoids, are the major components of the natural products isolated. Of the 82 metabolites, 75 compounds (91.5%) are briarane-type diterpenoids. Of the briaranes, 50 compounds are halogenated (50/75 = 66.7%). Briarane-type natural products are a large family of natural products that are only isolated from marine organisms and the compounds of this type were suggested originally synthesized from the 3,8-cyclization of cembranoids by the host corals and not by their zooxanthellae [37,53,54]. Briarane-type diterpenoids continue to attract attention owing to their complex structures and potential biomedical activities.

Studies on the novel substances for biomedical use from the marine invertebrates originally distributed in the Indo-Pacific Ocean will play an important role in natural product research [55]. Marine natural products currently under clinical trials are limited. Based on the potential medical use and complex structures, it is very difficult to obtain enough material for further studies by

chemical methods. How to make the best use of aquaculture technology to enhance in captivity mass production of raw materials needed for extraction of biomedical use marine natural compounds is very important in the future [56].

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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