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SURVEY OF BRIARANE-TYPE DITERPENOIDS – PART VII

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Abstract – The structures, names, bioactivities, and references of 78 briarane-type natural products, including 56 new metabolites, isolated between 2017 and 2019 are summarized in this review article. All the briarane diterpenoids mentioned in this review were isolated from the octocorals Alcyonacea belonging to genus *Briareum*; the Gorgonacea belonging to genus *Junceella* and

Subergorgia; and the Pennatulacea belonging to genus *Anthoptilum*. Some of these compounds exhibited potentially biomedical activities, including anti-inflammatory activity, antiviral activity, and cytotoxicity.

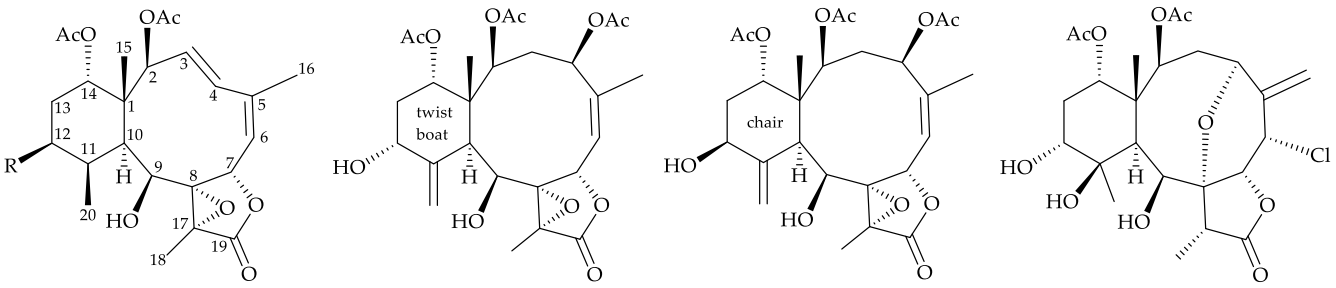
1. INTRODUCTION

Following previous review articles from our research group focused on marine-origin briarane-type natural products,[1–6] this review covers the literature from 2017 to 2019, and describes 78 naturally-occurring briarane-related diterpenoids (including 56 new metabolites), all of which are characterized by the presence of a γ-lactone moiety fused to a bicyclo[8.4.0] ring system, obtained from various octocorals, including *Briareum excavatum*, *Briareum violaceum*, *Junceella fragilis*, *Subergorgia suberosa*, and *Anthoptilum grandiflorum*. Many of these compounds exhibited bioactivities *in vitro*, which might indicate a potential for use in biomedical applications. This survey of briarane-related compounds is presented taxonomically according to genus and species.

2. ALCYONACEA

2-1. *Briareum excavatum* (family Briareidae)

In 1977, the first briarane diterpenoid, briarein A, was isolated from the Caribbean octocoral *B. asbestinum*,[7] and since then *Briareum* played the most important role to produce briarane-type natural products. In 2017, four new briaranes, briarenols B–E (**1**– **4**) (Figure 1), were isolated from *B. excavatum*, collected off the waters of Taiwan, and the structures of briaranes **1**–**4** were established by interpretation of spectroscopic data.[8,9] It is interesting to note that **1** was found to enhance the expression of iNOS and COX-2 (158 and 132%, respectively)[8] than those of its 12-*O*-*n*-butyryl analogue, briarenolide ZII (**5**) (47 and 90%, respectively),[8,10] at a concentration of 10 μM. It means that the size of functional groups at C-12 could influence the bioactivity. Briarenols D (**3**) and E (**4**) reduced the levels of iNOS to 78 and 67%, at a concentration of 10 μM, respectively, and **3** showed an inhibitory effect on the release of elastase with an IC_{50} value of 4.65 μM.[9]



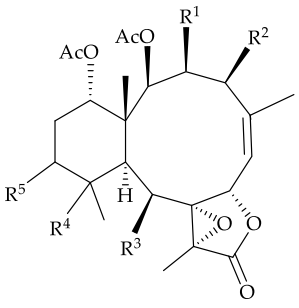
1: R = OH
5: R = OC(O)Pr-*n*

2 **3** **4**

Figure 1. Structures of briarenols B–E (**1**–**4**) and briarenolide ZII (**5**)

2-2. *Briareum violaceum*

In continuing studies of the chemical constituents of a cultured-type octocoral *B. violaceum*, 14 new briarane derivatives, briaviolides K–X (**6**–**19**),[11–15] as well as four known briaranes, excavatolide Z (**20**),[13,16] brianthein W (**21**),[14,17,18] excavatolides B (**22**) and E (**23**) (Figure 2),[15,19,20] were obtained, and the structures of new briaranes **6**–**19** were determined based on analysis of their spectroscopic data. In the anti-inflammatory activity test, briaviolide L (**7**) showed activity against the expressions of iNOS and COX-2 to 47 and 62%, respectively, but briaviolide K (**6**) was found to be inactive, indicating that the activity of these two compounds is dependent on the stereochemistry of 11-hydroxy group.[11] Furthermore, by comparison the inhibitory effects on the release of iNOS of **7** (47%) with that of briaviolide O (**10**) (11%),[11,12] suggested that the 4β-acetoxy group in **10** will enhance the inhibitory activity on the release of iNOS. It is also interesting to note that briaviolide Q (**12**) reduced the level of iNOS to 26% and its analogue, excavatolide Z (**20**),[16] was found to be more weak (66%), indicating the length of the acyl group at C-12 could influence the bioactivity.[13] Furthermore, briaviolide S (**14**) showed an inhibitory effect on the generation of superoxide anion with an IC_{50} value of 5.37 μM[14] and excavatolide B (**22**) could be potential use as a therapeutic agent through the inhibition of osteoclastogenesis in rheumatoid arthritis.[21] Briarane **22** was also found to enhance contextual memory retrieval in both wild-type and *Ca*$_v$*3.2*$^{-/-}$ mice via repressing the delayed rectifier potassium current in the hippocampus.[22] The absolute configurations for the known briaranes, brianthein W (**21**), excavatolides B (**22**) and E (**23**) were determined by single-crystal X-ray diffraction analysis in later studies,[14,15] and as briaranes **6**–**20** were obtained along with briaranes **21**–**23** from the same target organism, *B. violaceum*, it is reasonable on biogenetic grounds to assume that briaranes **6**–**23** have the same configuration as the C-15 methyl group *trans* to H-10, in briarane-related natural products.



6: $R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = \beta$-OH, $R^5 = \alpha$-OC(O)Pr-*n*
7: $R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = \alpha$-OH, $R^5 = \alpha$-OC(O)Pr-*n*
8: $R^1 = H$, $R^2 = R^3 = OAc$, $R^4 = \alpha$-H, $R^5 = \alpha$-OC(O)Pr-*n*
10: $R^1 = H$, $R^2 = R^3 = OAc$, $R^4 = \alpha$-OH, $R^5 = \alpha$-OC(O)Pr-*n*
11: $R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = \beta$-OH, $R^5 = \alpha$-OAc
12: $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = \beta$-OH, $R^5 = \alpha$-OC(O)$(CH_2)_4$Me
17: $R^1 = H$, $R^2 = OH$, $R^3 = OAc$, $R^4 = \beta$-OH, $R^5 = \alpha$-OC(O)Pr-*n*
20: $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = \beta$-OH, $R^5 = \alpha$-OC(O)Pr-*n*
22: $R^1 =$ OC(O)Pr-*n*, $R^2 = H$, $R^3 = OAc$, $R^4 = \alpha$-H, $R^5 = \beta$-OH
23: $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = \alpha$-H, $R^5 = \beta$-OH

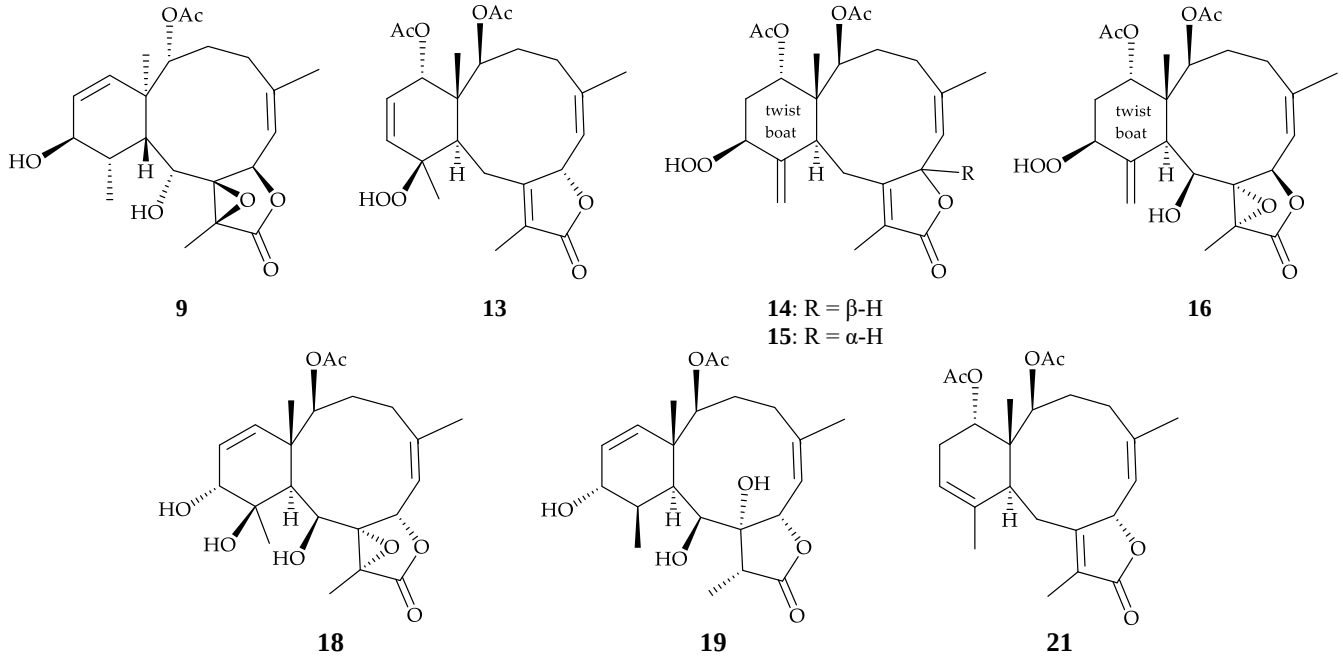


Figure 2. Structures of briaviolides K–X (**6**–**19**), excavatolides Z (**20**), B (**22**), E (**23**), and brianthein W (**21**)

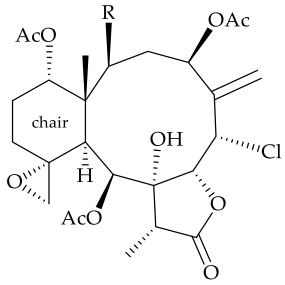
3. GORGONACEA

3-1. *Junceella fragilis* (family Ellisellidae)

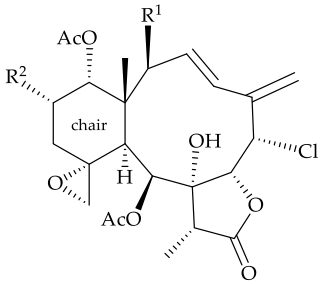
In 2017, 21 new briaranes, including fragilolides B–Q (**24**–**39**),[23] 3-deacetylpraelolide (**40**), 13α-acetoxy-3-deacetylpraelolide (**41**), 13α-acetoxy-2-deacetylpraelolide (**42**), 13α-acetoxy-3-deacetyljunceellin (**43**), and 13α-acetoxy-2-deacetyljunceellin (**44**),[24] along with three known briaranes, frajunolides H (**45**)[23,25] and N (**46**),[23,26] fragilide J (= 2-deacetylpraelolide) (**47**),[24,27] and a mixture of known metabolites 3-deacetyljunceellin (**48**) and 2-deacetyljunceellin (**49**),[24,28] were produced by *J. fragilis*, collected off the inner coral reef in Hainan Island, China (Figure 3).[23,24] Structures of briaranes **24**–**49** were elucidated by spectroscopic methods and by comparison the spectroscopic data of these compounds with those reported previously. Acetylation of **40** and **47** yield a crystal product, praelolide (**50**),[24,25,28–43] and its structure, including the absolute configuration of **50**, was further confirmed by a single-crystal X-ray diffraction analysis.[24] As the naturally-occurring briaranes **24**–**49** were isolated from the same organism, it is reasonable on biogenetic grounds to assume that briaranes **24**–**49** have the same configuration as that of **50** (praelolide).

Frajunolide H (**45**) was found to show cytotoxicity toward Hep G2 (human hepatocellular carcinoma), SMMC-7721 (human papillomavirus-related endocervical adenocarcinoma), BGC-823 (human papillomavirus-related endocervical adenocarcinoma), HGC-27 (human gastric carcinoma), MGC-803 (human mucinous gastric adenocarcinoma), NCI-H1650 (human minimally invasive lung adenocarcinoma), A2780 (human ovarian carcinoma), and PA-1 (human ovarian mixed germ cell tumor)

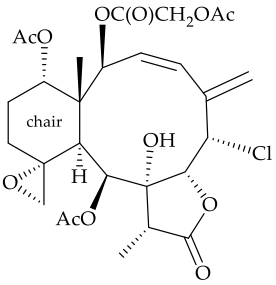
with IC_{50} values 0.89, 0.61, 2.10, 0.61, 1.97, 6.47, 1.18, and 0.42 μM, respectively, and fragilolides D (**26**), G (**29**), I (**31**), L (**34**), and P (**38**), and frajunolide N (**46**) exhibited 19.4, 31.3, 37.3, 30.2, 26.4, and 21.1% selective inhibitory effects toward hepatitis B e-antigen (HBeAg) at a concentration of 10 μM, respectively.[23] It is interesting to note that compounds **40** and **47**; **41** and **42**; **43** and **44**; **48** and **49** were obtained as equilibrium mixtures, respectively, and at a dose of 50 μM, the mixtures of **40** and **47**; **41** and **42**; **43** and **44**; and **48** and **49**, exerted inhibitory activities against the NO production with inhibitory rates of 39.4, 46.4, 42.7, and 36.3%, respectively.[24]



24: R = OC(O)Et
46: R = OAc



25: R^1 = OC(O)Et, R^2 = OAc
26: R^1 = OAc, R^2 = H



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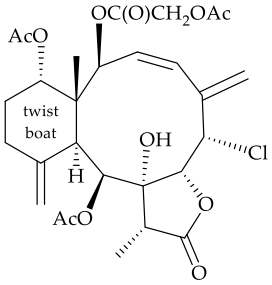

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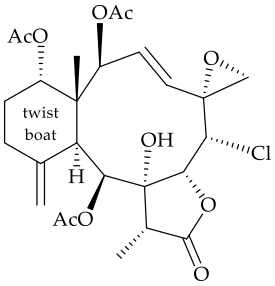

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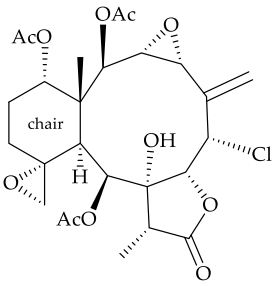

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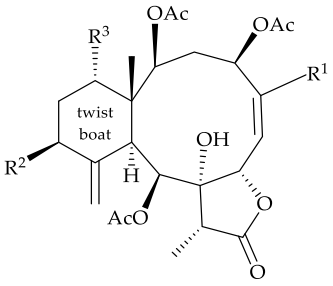
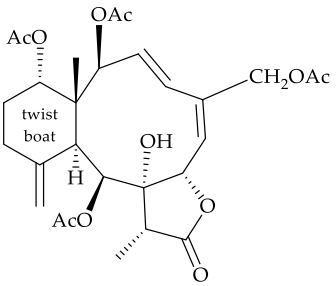


31: R^1 = Me, R^2 = R^3 = OAc
32: R^1 = Me, R^2 = H, R^3 = OC(O)Bu-*i*
33: R^1 = CH_2Cl, R^2 = H, R^3 = OAc



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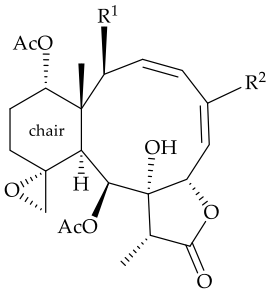
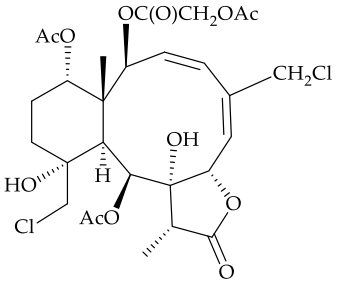


35: R^1 = $OC(O)CH_2OAc$, R^2 = CH_2OAc
36: R^1 = $OC(O)CH_2OC(O)Bu$-*i*, R^2 = CH_2OAc
37: R^1 = $OC(O)CH_2OC(O)Bu$-*i*, R^2 = CH_2Cl



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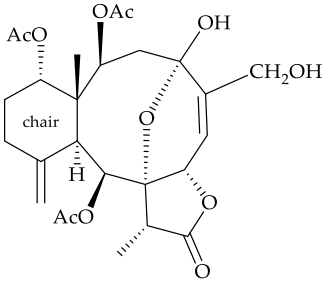

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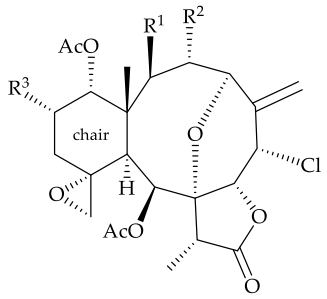
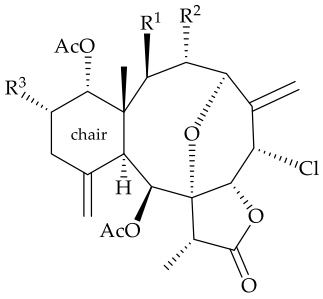


40: R^1 = OAc, R^2 = OH, R^3 = H
41: R^1 = R^3 = OAc, R^2 = OH
42: R^1 = OH, R^2 = R^3 = OAc
47: R^1 = OH, R^2 = OAc, R^3 = H
50: R^1 = R^2 = OAc, R^3 = H



43: R^1 = R^3 = OAc, R^2 = OH
44: R^1 = OH, R^2 = R^3 = OAc
48: R^1 = OAc, R^2 = OH, R^3 = H
49: R^1 = OH, R^2 = OAc, R^3 = H

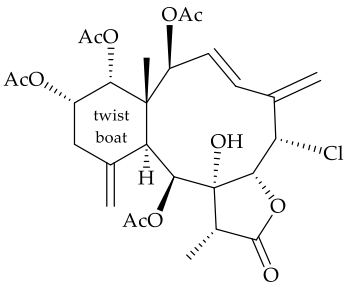


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Figure 3. Structures of fragilolides B–Q (**24**–**39**), 3-deacetylpraelolide (**40**), 13α-acetoxy-3-deacetyl-praelolide (**41**), 13α-acetoxy-2-deacetylpraelolide (**42**), 13α-acetoxy-3-deacetyljunceellin (**43**), and frajunolide N (**46**), fragilide J (**47**), 3-deacetyljunceellin (**48**), 2-deacetyljunceellin (**49**), and praelolide (**50**)

In addition, 14 new briaranes, (+)-12-*epi*-fragilide G (**51**)[44] and fragilides K–W (**52**–**64**),[43,45–48] as well as nine known briaranes, praelolide (**50**) (Figure 3),[24,25,28–43] gemmacolides V (**65**) and X (**66**),[41,43] juncins P (**67**),[36,43] Z (**68**),[46,49] and ZI (**69**),[43,49] junceellin (**70**),[25,28,31–40,42,45,48,50,51] robustolide F (**71**),[46,52,53] and junceellonoid D (**72**),[37,48,54] were isolated from *J. fragilis*, collected off the waters of Taiwan (Figure 4).[43–48] The structures of all isolates **50**–**72** were established by spectroscopic methods and the absolute configuration of junceellin (**70**) was further confirmed by a single-crystal X-ray diffraction analysis.[45,51] Fragilides S (**60**) and T (**61**) are the first two briaranes known to possess 8α-hydroxy and 17β-methyl groups in the γ-lactone moieties.[47] Briarane **51** was found to be the enantiomer of (–)-12-*epi*-fragilide G (**73**)[55] and **73** showed a 74.5% inhibitory effect on human neutrophils in terms of the generation of superoxide anions at a concentration of 20 μM, but briarane **51** was not active. This result implied that the configurations of **51** and **73** played an important role in determining the activity.[44] Anti-inflammatory activity analysis showed that (+)-12-*epi*-fragilide G (**51**), fragilides L (**53**), S (**60**), U (**62**), and W (**64**), gemmacolide X (**66**), juncin ZI (**69**), and junceellin (**70**) inhibited iNOS expression to 54.7, 49.1, 61.2, 55.9, 28.6, 36.2, 43.3, 33.7%;[43,44,47,48] and gemmacolides V (**65**) and X (**66**) elicited reduction of COX-2 to 47.5 and 43.6%, at a concentration of 10 μM, in LPS-stimulated murine macrophage-like RAW264.7 cells, respectively.[43] Briarane **68** (juncin Z) showed a 25.6% inhibitory effect on the generation of superoxide anions by human neutrophils at a concentration of 10 μM.[46]

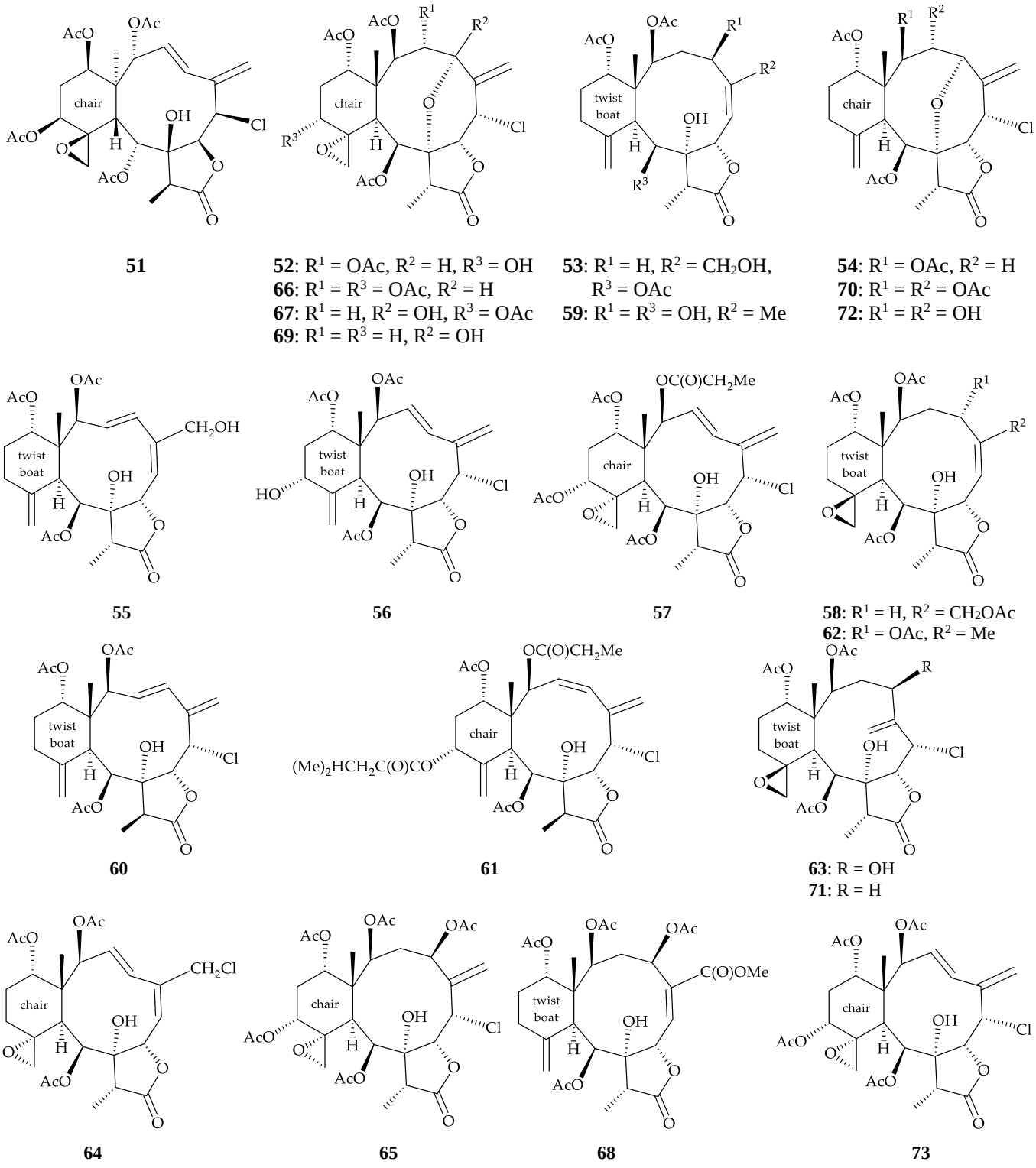
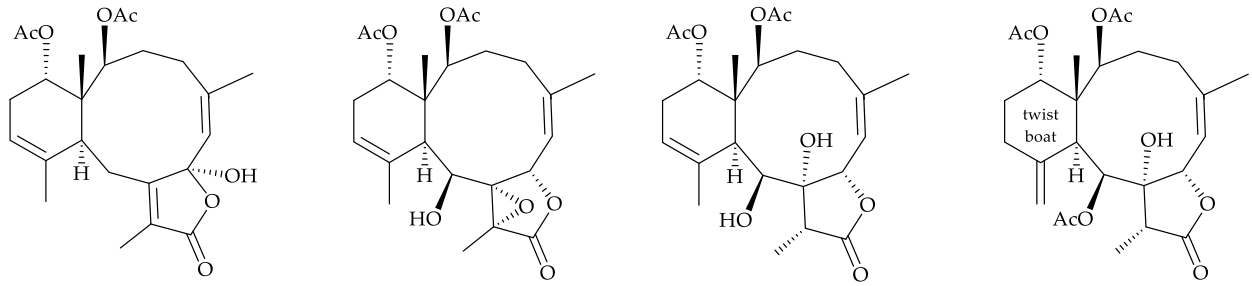


Figure 4. Strucutres of (+)-12-*epi*-fragilide G (**51**), fragilides K–W (**52**–**64**), gemmacolides V (**65**) and X (**66**), juncins P (**67**), Z (**68**), and ZI (**69**), junceellin (**70**), robustolide F (**71**), junceellonoid D (**72**), and (–)-12-*epi*-fragilide G (**73**)

3-2. *Subergorgia suberosa* (family Subergorgiidae)

In 2014, Sun *et al.* reported the isolation of five known briaranes, brianthein W (**21**) (Figure 2),[14,17,18] funicolide E (**74**),[56] 9-deacetylbriareolide H (**75**),[18,57,58] 9-deacetylstylatulide lactone (**76**),[18] and

umbraculolide A (**77**),[32,59] from the South China Sea gorgonian coral, *S. suberosa* (Figure 5).[60] Structural determination of known briaranes **21** and **74**–**77** were conducted using spectroscopic methods and by comparison with the spectral data previously reported in literature. The hydroxy group at C-7 in briarane **74** shown in ref.[60] should be revised as α-oriented as shown in Figure 5. An exocyclic double bond between C-11/20 was existed in umbraculolide A (**77**),[32,59] and based on this finding, the structure for umbraculolide A that shown in ref.[60] also should be revised as shown in Figure 5. Briarane **75** exhibited cytotoxicity toward A549 (human epithelial lung carcinoma) cells with an IC_{50} value of 26.7 μM.[60]



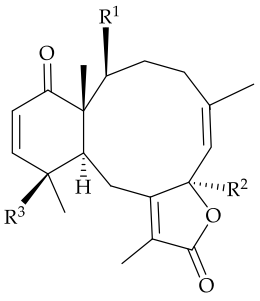
74 **75** **76** **77**

Figure 5. Strucutres of funicolide E (**74**), 9-deacetylbriareolide H (**75**), 9-deacetylstylatulide lactone (**76**), and umbraculolide A (**77**)

4. PENNATULACE

4-1. *Anthoptilum grandiflorum* (family Anthoptilidae)

Investigation of the chemical constituents of *A. grandiflorum*, collected off the north of Burdwood Bank by trawling on the R/V Nathaniel B. Palmer, the U.S. Antarctic Programs' research ship, afforded three novel briaranes, bathyptilones A–C (**78**–**80**) (Figure 6).[61] The structures, including the absolute configurations of briaranes **78**–**80** were elucidated by interpretation of spectroscopic methods, and futher confirmed by signle-crystal X-ray diffractions analysis. Briarane **78** showed cytotoxicity towad NTREA-2 (NT2) (human malignant pluripotent embryonal carcinoma) with an IC_{50} of 29 nM and briarane **80** was found to be more inactive in terms of cytotoxicity toward NT2 cells, indicating that the cytotoxicity of these compounds are largely dependent on the functional group at C-7.



78: R^1 = H, R^2 = R^3 = OH
79: R^1 = OAc, R^2 = OH, R^3 = H
80: R^1 = R^2 = H, R^3 = OH

Figure 6. Structures of bathyptilones A–C (**78**–**80**)

5. CONCLUSIONS

In the past three years, 78 briarane-type diterpenoids, including 56 new metabolites have been prepared from soft corals belonging to the orders Alcyonacea, Gorgonacea, and Pennatulacea and compounds of this type have been demonstrated to possess various bioactivities, for example, excavatolide B (**22**) has been proven to show anti-inflammatory and to enhance contextual memory retrieval and bathyptilone A (**78**) showed potential cytotoxicity. Because of the structural diversity and biomedical bioactivities, there have been little synthetic work on briarane analogues.[62–65] It is interesting to note that most briaranes, excepting bathyptilones A–C (**78**–**80**), reported as having been isolated between 2017 and 2019 were all collected from octocorals distributed in the South China Sea.

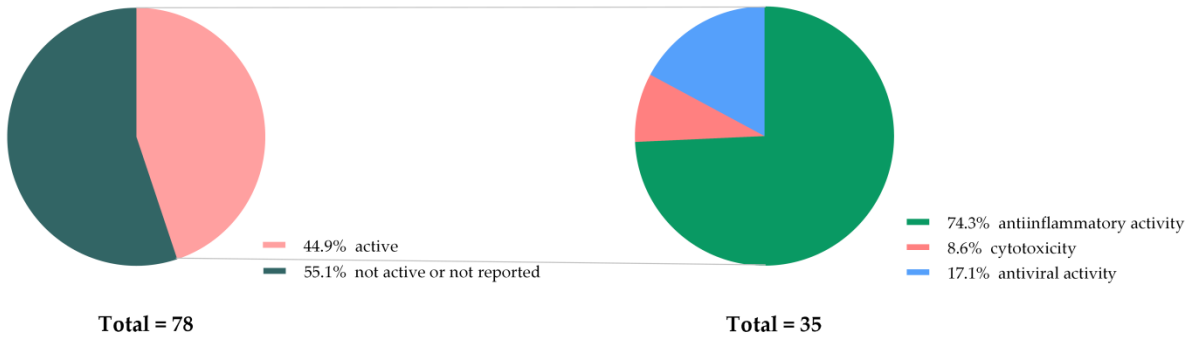


Figure 7. Numbers of briarane-type diterpnoids between 2017–2019 and their biomedical activities

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