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SURVEY OF BRIARANE-RELATED DITERPENOIDS⁻ PART II

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Abstract – The structures, names, biological activity, and references of sixty-six new briarane-related diterpenoids are described in this mini-review. All briaranes are obtained from Gorgonacea (genus *Briareum*, *Erythropodium*, *Ellisella*, and *Junceella*) and Pennatulacea (genus *Cavernularia* and *Pteroeides*). Some of these natural products showed potential biological activity.

1. INTRODUCTION

In the past three years,[1] sixty-six new briarane-related natural products, which most are characterized by the presence of a γ-lactone fused to a bicyclo[8.4.0] ring system, were isolated from various octocorals, mainly including the gorgonian corals *Briareum asbestinum*, *B. excavatum*, *B. stechei*, *Junceella fragilis*, *J. juncea*, *Erythropodium caribaeorum* and the sea pen corals identified as *Cavernularia* sp. and *Pteroeides* sp., respectively. Some of these compounds showed interesting biological activity, such as cytotoxicity and reversal of multidrug resistance. This survey of briarane-related compounds will be presented taxonomically according to genus and species.

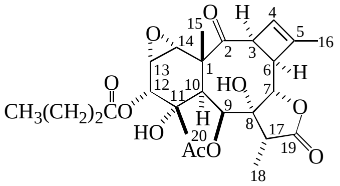
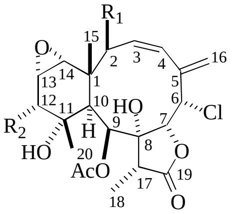
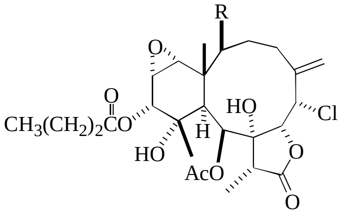
2. GORGONACEA

2.1. *Briareum* (family Briareidae)

A. *Briareum asbestinum*

Gorgonian corals of the genus *Briareum*, which are distributed extensively on West Indian waters and the subtropical and tropical waters of Indo-Pacific Ocean, have been investigated and yielded a number of secondary metabolites, including pyranone, briarane, eunicellin, cembrane-type compounds and the marine toxin, palytoxin.[1,2] In the continuing research on the Caribbean gorgonian corals, the coral *B. asbestinum*, collected at Sweetings Cay in the Bahamas were studied, and six novel metabolites, including a C20-rearranged briarane possessing tricyclo[8.4.0.0^{3,6}]tetradec-4-ene ring system, cyclobutenbriarein A (**1**), and five briaranes, 11-hydroxybrianthein V (**2**), 11-hydroxybrianthein U (**3**), 11-hydroxybrianthein Y (**4**), 3,4-dihydro-11-hydroxybrianthein V (**5**), and 3,4-dihydro-11-hydroxybrianthein U (**6**), were isolated. The structures of metabolites (**1**–**6**) were elucidated by extensive spectroscopic methods (IR, MS, ^{1}H, and ^{13}C NMR spectrum). The stereostructure, including the absolute configuration, of 11-hydroxybrianthein V (**2**) was further confirmed by X-Ray analysis. It is important to note that cyclobutenbriarein A (**1**) is the first natural product possessing a tricyclo[8.4.0.0^{3,6}]tetradec-4-ene ring system.[3]

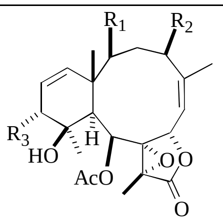
Table 1. The Briarane-Related Metabolites from *B. asbestinum*

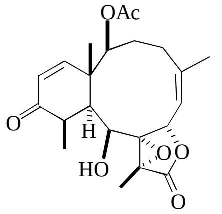
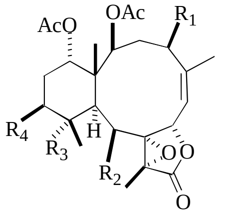
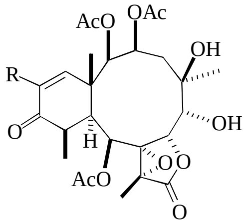
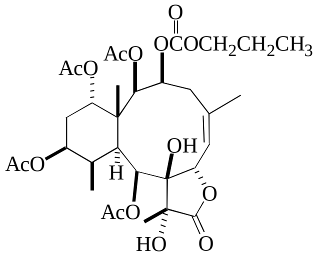
Structure	No.	Name	Ref.
	**1**	cyclobutenbriarein A	3
	**2** **3** **4**	11-hydroxybrianthein V (R$_1$ = R$_2$ = OCO(CH$_2$)$_2$CH$_3$) 11-hydroxybrianthein U (R$_1$ = OAc, R$_2$ = OCO(CH$_2$)$_2$CH$_3$) 11-hydroxybrianthein Y (R$_1$ = OCO(CH$_2$)$_2$CH$_3$, R$_2$ = OAc)	3 3 3
	**5** **6**	3,4-dihydro-11-hydroxybrianthein V (R = OCO(CH$_2$)$_2$CH$_3$) 3,4-dihydro-11-hydroxybrianthein U (R = OAc)	3 3

B. *Briareum excavatum*

Eight new briaranes, briaexcavatolides S–Z (**7**–**14**), were obtained from the Taiwanese gorgonian coral *B. excavatum*. The relative stereostructures of these metabolites were established by the interpretations of spectral data analysis (IR, UV, MS, ^{1}H, and ^{13}C NMR spectrum).[4–6] The configuration of briaexcavatolide X (**12**) was further confirmed by minimum molecular mechanics calculations.[6] It has to be noted that a briarane containing a six-membered ring with an α-hydroxy-α,β-unsaturated ketone functional group, as presented in **12**, is unprecedential.[6]

Table 2. The Briarane-Type Metabolites from *B. excavatum*

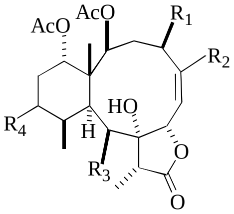
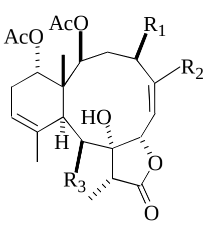
Structure	No.	Name	Ref.
	**7** **11**	briaexcavatolide S (R$_1$ = OH, R$_2$ = R$_3$ = OAc) briaexcavatolide W (R$_1$ = OAc, R$_2$ = OH, R$_3$ = OCO(CH$_2$)$_2$CH$_3$)	4 5

Structure	No.	Name	Ref.
	**8**	briaexcavatolide T	4
	**9**	briaexcavatolide U ($R_1 = R_2 = OAc$, $R_3 = R_4 = OH$)	4
	10	briaexcavatolide V ($R_1 = R_3 = H$, $R_2 = OH$, $R_4 = OCO(CH_2)_2CH_3$)	4
	**12**	briaexcavatolide X (R = OH)	6
	13	briaexcavatolide Y (R = H)	6
	**14**	briaexcavatolide Z	6

C. *Briareum stechei*

Twelve new briarane-type metabolites, including milolides G–N (**15**–**22**), 16-acetoxymilolide G (**23**), 16-hydroxymilolide M (**24**), 16-acetoxymilolide M (**25**), and 16-acetoxymilolide N (**26**), were obtained from the Western Pacific Ocean gorgonian *B. stechei*, collected at Mil Channel, Yap, Federated States of Micronesia. The relative stereostructures of briaranes (**15**–**26**) were established by spectral data (MS, ^1H, and ^{13}C NMR spectrum).[7]

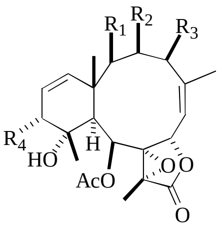
Table 3. The Briarane-Type Metabolites from *B. stechei*

Structure	No.	Name	Ref.
	**15**	milolide G ($R_1 = R_3 = OAc$, $R_2 = CH_3$, $R_4 = \beta$-OH)	7
	16	milolide H ($R_1 = H$, $R_2 = CH_2OAc$, $R_3 = OH$, $R_4 = \alpha$-OAc)	7
	17	milolide I ($R_1 = H$, $R_2 = COOCH_3$, $R_3 = OAc$, $R_4 = \beta$-OH)	7
	18	milolide J ($R_1 = R_3 = OAc$, $R_2 = COOCH_3$, $R_4 = \beta$-OH)	7
	23	16-acetoxymilolide G ($R_1 = R_3 = OAc$, $R_2 = CH_2OAc$, $R_4 = \beta$-OH)	7
	**19**	milolide K ($R_1 = H$, $R_2 = CH_2OAc$, $R_3 = OH$)	7
	20	milolide L ($R_1 = H$, $R_2 = CH_2Cl$, $R_3 = OH$)	7
	21	milolide M ($R_1 = R_3 = OAc$, $R_2 = CH_3$,)	7
	22	milolide N ($R_1 = OCO(CH_2)_2CH_3$, $R_2 = CH_3$, $R_3 = OAc$)	7
	24	16-hydroxymilolide M ($R_1 = R_3 = OAc$, $R_2 = CH_2OH$)	7
	25	16-acetoxymilolide M ($R_1 = R_3 = OAc$, $R_2 = CH_2OAc$)	7
	26	16-acetoxymilolide N ($R_1 = OCO(CH_2)_2CH_3$, $R_2 = CH_2OAc$, $R_3 = OAc$)	7

D. *Briareum* sp.

The chemical constituents of a gorgonian coral belonging to the genus *Briareum*, collected at Amami Island, Kagoshima Prefecture, Japan, were studied. Eight new briaranes, which are designated as briarlides A–H (**27**–**34**), were obtained from this organism. The relative stereostructures of briaranes (**27**–**34**) were determined by the interpretation of spectral data analysis (IR, MS, ^{1}H, and ^{13}C NMR spectrum). All briaranes (**27**–**34**) possess a double bond between C-13 and C-14. The cytotoxicity and structure activity relationships of briarlides A–H (**27**–**34**) toward the African green monkey kidney (Vero) and Madin-Daby Canine Kidney (MDCK) cells are described in the literature.[8]

Table 4. The Briarane-Type Metabolites from *Briareum* sp.

Structure	No.	Name	Biological Activity	Ref.
	**27**	briarlide A ($R_1 = R_2 = R_3 = R_4 = OAc$)	CC_{50} (Vero, MDCK) = 2.07, 4.74 μg/mL	8
	28	briarlide B ($R_1 = R_3 = R_4 = OAc$, $R_2 = OH$)	CC_{50} (Vero, MDCK) = 18.9, 15.4 μg/mL	8
	29	briarlide C ($R_1 = R_2 = OH$, $R_3 = R_4 = OAc$)	CC_{50} (Vero, MDCK) = 62.1, 38.6 μg/mL	8
	30	briarlide D ($R_1 = R_4 = OAc$, $R_2 = OH$, $R_3 = OCO(CH_2)_6CH_3$)	CC_{50} (Vero, MDCK) = 2.26, 2.49 μg/mL	8
	31	briarlide E ($R_1 = R_4 = OAc$, $R_2 = OH$, $R_3 = OCO(CH_2)_4CH_3$)	CC_{50} (Vero, MDCK) = 4.24, 4.91 μg/mL	8
	32	briarlide F ($R_1 = R_4 = OAc$, $R_2 = OCO(CH_2)_6CH_3$, $R_3 = OH$)	CC_{50} (Vero, MDCK) = 4.26, 3.49 μg/mL	8
	33	briarlide G ($R_1 = R_2 = R_4 = OAc$, $R_3 = H$)	CC_{50} (Vero, MDCK) = 22.2, 67.1 μg/mL	8
	34	briarlide H ($R_1 = R_4 = OH$, $R_2 = OAc$, $R_3 = H$)	CC_{50} (Vero, MDCK) = > 100, > 100 μg/mL	8

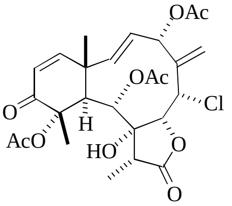
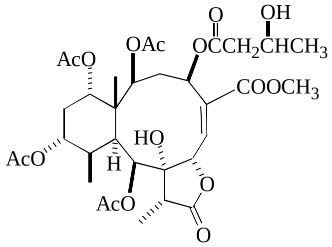
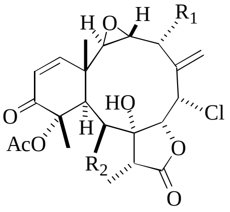
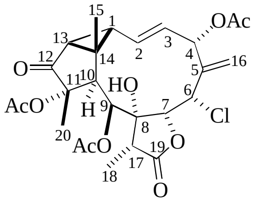
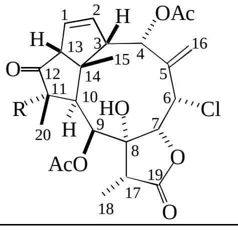
2.2. *Erythropodium* (family Briareidae)

A. *Erythropodium caribaeorum*

In the continuing researches for *E. caribaeorum*, a series of novel briarane-related metabolies, including erythrolides K–Q,[9] erythrolides R–V (**35**–**39**),[10] and aquariolides A–C (**40**–**42**),[10,11] have been isolated from *E. caribaeorum*, collected in Dominica. The structures of metabolites (**35**–**42**) were elucidated by extensive spectral analysis (IR, UV, MS, ^{1}H, and ^{13}C NMR spectrum). In addition, the structure and absolute configuration of erythrolide S (**36**), were determined by chemical transformation. This metabolite is also the first briarane derivative to bear a 3-hydroxybutanoyl substituent. Erythrolide T (**37**) is the first erythrolide to possess a 2,3-epoxy and an acetoxyl functionality at C-4, respectively.

The biosynthetic pathway of the metabolites such as aquariolides A–C (**40**–**42**), which possess the auqariane skeleton, can be formally derived from the briarane skeleton by sequential di-π-methane and vinyl-cyclopropane rearrangements.[11] Aquariolides B (**41**) and C (**42**) showed intermediate activity toward MCF-7 (human breast cancer) cells.[10] Due to all the erythrolide and aquariolide metabolites are only found in the Caribbean gorgonian coral *E. caribaeorum* and on basis of the special structural features of the compounds of these two types, the erythrolide and aquariolide derivatives may well be chemotaxonomic markers for *E. caribaeorum*.[1,9–11]

Table 5. The Briarane-Related Metabolites from *E. caribaeorum*

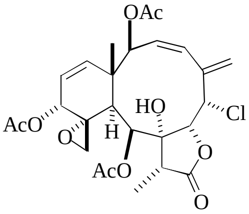
Structure	No.	Name	Ref.
	**35**	erythrolide R	10
	**36**	erythrolide S	10
	**37** **38**	erythrolide T ($R_1 = R_2 = OAc$) erythrolide U ($R_1 = H, R_2 = OCOCH_2OH$)	10 10
	**39**	erythrolide V	10
	**40** **41** **42**	aquariolide A (R = OH) aquariolide B ($R = OCH_3$) aquariolide C (R = OAc)	11 10 10

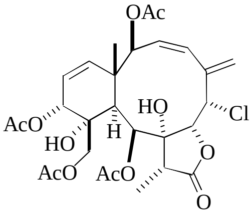
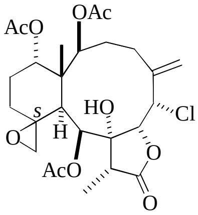
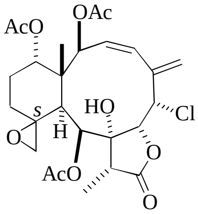
2.3. *Ellisella* (family Ellisellidae)

A. *Ellisella* sp.

The investigation on the chemical constituents of a gorgonian coral belonging to the genus *Ellisella*, collected in Okinawa, Japan, has afforded four unnamed new briaranes (**43–46**). The relative stereostructures of briaranes (**43–46**) were elucidated by analysis of spectral data (IR, MS, ^{1}H, and ^{13}C NMR spectrum). Briarane (**44**) is the first briarane metabolite possessing a 20-acetoxyl group. Briaranes (**44** and **45**) showed activity to inhibit the formation of cytokinesis on NBT-II cells.[12]

Table 6. The Briarane-Type Metabolites from *Ellisella* sp.

Structure	No.	Biological Activity	Ref.
	**43**		12

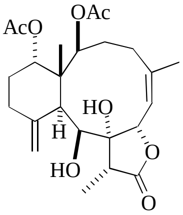
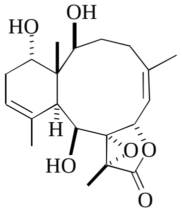
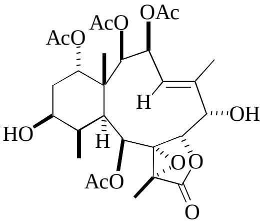
Structure	No.	Biological Activity	Ref.
	**44**	inhibited cytokinesis, causing multinuclei formation on NBT-II cells at 0.5 μg/mL	12
	**45**	inhibited cytokinesis, causing multinuclei formation on NBT-II cells at 2 μg/mL	12
	**46**		12

2.4. ***Junceella*** (family Ellisellidae)

A. ***Junceella fragilis***

Three new briaranes, 9-*O*-deacetylumbraculolide A (**47**),[13] junceellolide H (**48**),[14] fragilide A (**49**),[15] and two known metabolites, praelolide and junceellin,[14,16] were isolated from the gorgonian coral, *Junceella fragilis*, collected off the southern Taiwan coast. The relative stereostructures of the new metabolites (**47**–**49**), were elucidated by extensive spectroscopic methods (IR, Ms, ^{1}H, and ^{13}C NMR spectrum), particularly in 2D NMR studies. Fragilide A (**49**) is the first briarane derivative possessing a 6-hydroxyl group.[15]

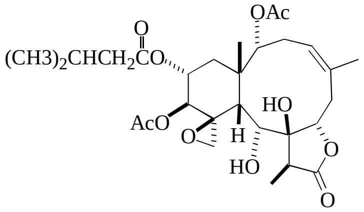
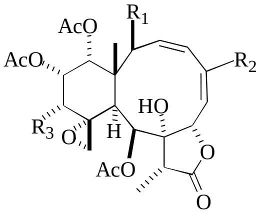
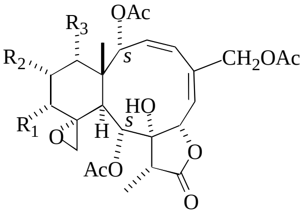
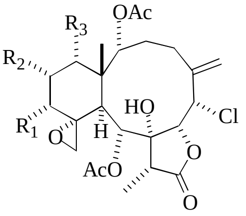
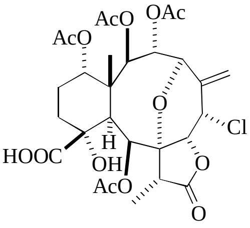
Table 7. The Briarane-Type Metabolites from *J. fragilis*

Structure	No.	Name	Ref.
	**47**	9-*O*-deacetylumbraculolide A	13
	**48**	junceellolide H	14
	**49**	fragilide A	15

B. *Junceella juncea*

In addition to *J. fragilis*, *J. junea* also is a species distributed extensively on the Indo-Pacific Ocean. Thirteen briaranes, including eleven new metabolites, juncenolide B (**50**),[17,18] juncenolides B–E (**51**–**54**),[18–20] and juncins I–N (**55**–**60**),[21,22] along with two known diterpenoids junceellin and praelolide,[16] were obtained from the gorgonian coral *J. juncea*, collected off Indian Ocean (briaranes **50** and **55**–**59**) and southern Taiwan coast (briaranes **51**–**54** and **60**), respectively. The relative stereostructures of briaranes (**50**–**60**) were determined by extensive spectral data analysis (IR, UV, MS, ^{1}H, and ^{13}C NMR spectrum). Juncin N (**60**) is the first briarane metabolite containing a carboxyl acid group.[22] In the cytotoxic activity testing, juncenolide C (**52**) exhibited mild cytotoxicity against the growth of human hepa adenocarcinoma (HEPA 59T/VGH) and oral epidermoid carcinoma (KB-16) cells.[19]

Table 8. The Briarane-Type Metabolites from *J. juncea*

Structure	No.	Name	Biological Activity	Ref.
	**50**	juncenolide B		17,18
	**51**	juncenolide B (R_1 = OAc, R_2 = CH_2OH, R_3 = H)		18,19
	52	juncenolide C (R_1 = R_3 = OAc, R_2 = CH_2OH)	IC_{50} (HEPA 59T/VGH, KB-16) = 6.6, 7.8 μg/mL	19
	53	juncenolide D (R_1 = R_3 = OAc, R_2 = CH_2OCH_3)		19
	54	juncenolide E (R_1 = $OCOCH_2CH(CH_3)_2$, R_2 = CH_2OH, R_3 = H)		20
	**55**	juncin I (R_1 = R_3 = OAc, R_2 = $OCOCH_2CH(CH_3)_2$)		21
	56	juncin J (R_1 = R_2 = $OCOCH_2CH(CH_3)_2$, R_3 = OAc,)		21
	57	juncin K (R_1 = R_3 = $OCOCH_2CH(CH_3)_2$, R_2 = H)		21
	**58**	juncin L (R_1 = R_2 = $OCOCH_2CH(CH_3)_2$, R_3 = OAc)		21
	59	juncin M (R_1 = R_3 = $OCOCH_2CH(CH_3)_2$, R_2 = H)		21
	**60**	juncin N		22

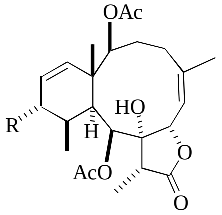
3. PENNATULACEA

3.1. *Cavernularia* (family Veretillidae)

A. *Cavernularia* sp.

Marine coelenterates of the order Pennatulacea have been proven to be rich sources of diterpenoids featuring the skeletal class of briaranes.[1] Two new briaranes, cavernulins A (**61**) and B (**62**), were isolated from an Indian Ocean sea pen coral, which is identified as *Cavernularia* sp., collected from the Eastern Coast of Bay of Bengal. The relative stereostructures of metabolites (**61** and **62**) were elucidated on the basis of spectral evidences (IR, MS, ^{1}H and ^{13}C NMR spectrum).[23]

Table 9. The Briarane-Type Metabolites from *Cavernularia* sp.

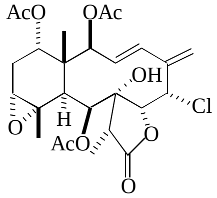
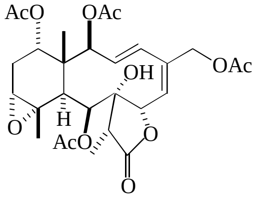
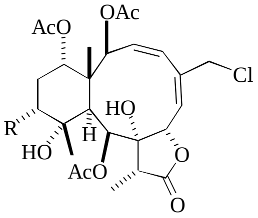
Structure	No.	Name	Ref.
	**61**	cavernulin A (R = $OCO(CH_2)_2CH_3$)	23
	62	cavernulin B (R = OH)	23

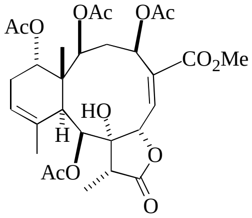
3.2. *Pteroeides* (family Pteroeidae)

A. *Pteroeides* sp.

An Indonesian sea pen coral identified as *Pteroeides* sp., has afforded four new unnamed briarane-type diterpenoids (**63–66**). The relative stereostructures of briaranes (**63–66**) were determined on the basis of their spectral data (IR, MS, ^{1}H, and ^{13}C NMR spectrum).[12] The metabolites (**63–65**) were inactive in the screening for multidrug resistance against oral epidermoid carcinoma KB-C2 (P-Gp type) and KB-CV60 (MRP-1 type) cells.[12,24]

Table 10. The Briarane-Type Metabolites from *Pteroeides* sp.

Structure	No.	Name	Ref.
	**63**		12
	**64**		12
	**65**	R = $OCOCH_2CH_3$	12

Structure	No.	Name	Ref.
	**66**		12

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