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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

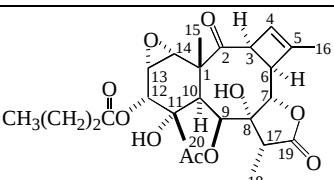
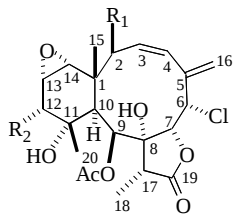
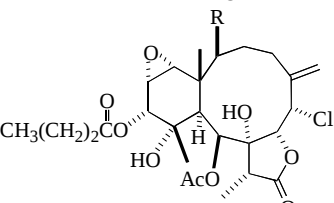
2.1. *Briareum* (family Briareidae)

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, ¹H, and ¹³C 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

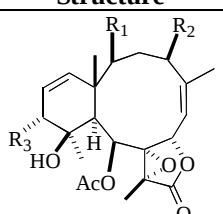
Table 1. The Briarane-Related Metabolites from *B. asbestinum*

Structure	No.	Name	Ref.
	1	cyclobutenbriarein A	3
	2	11-hydroxybrianthein V (R ₁ = R ₂ = OCO(CH ₂) ₂ CH ₃)	3
	3	11-hydroxybrianthein U (R ₁ = OAc, R ₂ = OCO(CH ₂) ₂ CH ₃)	3
	4	11-hydroxybrianthein Y (R ₁ = OCO(CH ₂) ₂ CH ₃ , R ₂ = OAc)	3
	5	3,4-dihydro-11-hydroxybrianthein V (R = OCO(CH ₂) ₂ CH ₃)	3
	6	3,4-dihydro-11-hydroxybrianthein U (R = OAc)	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, ¹H, and ¹³C 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 unprecedented.⁶

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

Structure	No.	Name	Ref.
	7	briaexcavatolide S (R ₁ = OH, R ₂ = R ₃ = OAc)	4
	11	briaexcavatolide W (R ₁ = OAc, R ₂ = OH, R ₃ = OCO(CH ₂) ₂ CH ₃)	5

Structure	No.	Name	Ref.
	8	briaexcavatulide T	4
	9	briaexcavatulide U ($R_1 = R_2 = \text{OAc}$, $R_3 = R_4 = \text{OH}$)	4
	10	briaexcavatulide V ($R_1 = R_3 = \text{H}$, $R_2 = \text{OH}$, $R_4 = \text{OCO}(\text{CH}_2)_2\text{CH}_3$)	4
	12	briaexcavatulide X ($R = \text{OH}$)	6
	13	briaexcavatulide Y ($R = \text{H}$)	6
	14	briaexcavatulide 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

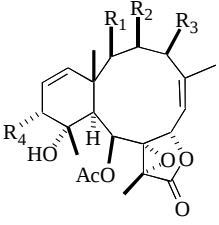
Table 3. The Briarane-Type Metabolites from *B. stechei*

Structure	No.	Name	Ref.
	15	milolide G ($R_1 = R_3 = \text{OAc}$, $R_2 = \text{CH}_3$, $R_4 = \beta\text{-OH}$)	7
	16	milolide H ($R_1 = \text{H}$, $R_2 = \text{CH}_2\text{OAc}$, $R_3 = \text{OH}$, $R_4 = \alpha\text{-OAc}$)	7
	17	milolide I ($R_1 = \text{H}$, $R_2 = \text{COOCH}_3$, $R_3 = \text{OAc}$, $R_4 = \beta\text{-OH}$)	7
	18	milolide J ($R_1 = R_3 = \text{OAc}$, $R_2 = \text{COOCH}_3$, $R_4 = \beta\text{-OH}$)	7
	23	16-acetoxymilolide G ($R_1 = R_3 = \text{OAc}$, $R_2 = \text{CH}_2\text{OAc}$, $R_4 = \beta\text{-OH}$)	7
	19	milolide K ($R_1 = \text{H}$, $R_2 = \text{CH}_2\text{OAc}$, $R_3 = \text{OH}$)	7
	20	milolide L ($R_1 = \text{H}$, $R_2 = \text{CH}_2\text{Cl}$, $R_3 = \text{OH}$)	7
	21	milolide M ($R_1 = R_3 = \text{OAc}$, $R_2 = \text{CH}_3$)	7
	22	milolide N ($R_1 = \text{OCO}(\text{CH}_2)_2\text{CH}_3$, $R_2 = \text{CH}_3$, $R_3 = \text{OAc}$)	7
	24	16-hydroxymilolide M ($R_1 = R_3 = \text{OAc}$, $R_2 = \text{CH}_2\text{OH}$)	7
	25	16-acetoxymilolide M ($R_1 = R_3 = \text{OAc}$, $R_2 = \text{CH}_2\text{OAc}$)	7
	26	16-acetoxymilolide N ($R_1 = \text{OCO}(\text{CH}_2)_2\text{CH}_3$, $R_2 = \text{CH}_2\text{OAc}$, $R_3 = \text{OAc}$)	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 briaralides 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, ^1H , 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 briaralides A–H (27–34) toward the African green monkey kidney (Vero) and Madin-Darby 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	briaralide A ($R_1 = R_2 = R_3 = R_4 = \text{OAc}$)	CC_{50} (Vero, MDCK) = 2.07, 4.74 $\mu\text{g/mL}$	8
	28	briaralide B ($R_1 = R_3 = R_4 = \text{OAc}$, $R_2 = \text{OH}$)	CC_{50} (Vero, MDCK) = 18.9, 15.4 $\mu\text{g/mL}$	8
	29	briaralide C ($R_1 = R_2 = \text{OH}$, $R_3 = R_4 = \text{OAc}$)	CC_{50} (Vero, MDCK) = 62.1, 38.6 $\mu\text{g/mL}$	8
	30	briaralide D ($R_1 = R_4 = \text{OAc}$, $R_2 = \text{OH}$, $R_3 = \text{OCO}(\text{CH}_2)_6\text{CH}_3$)	CC_{50} (Vero, MDCK) = 2.26, 2.49 $\mu\text{g/mL}$	8
	31	briaralide E ($R_1 = R_4 = \text{OAc}$, $R_2 = \text{OH}$, $R_3 = \text{OCO}(\text{CH}_2)_4\text{CH}_3$)	CC_{50} (Vero, MDCK) = 4.24, 4.91 $\mu\text{g/mL}$	8
	32	briaralide F ($R_1 = R_4 = \text{OAc}$, $R_2 = \text{OCO}(\text{CH}_2)_6\text{CH}_3$, $R_3 = \text{OH}$)	CC_{50} (Vero, MDCK) = 4.26, 3.49 $\mu\text{g/mL}$	8
	33	briaralide G ($R_1 = R_2 = R_4 = \text{OAc}$, $R_3 = \text{H}$)	CC_{50} (Vero, MDCK) = 22.2, 67.1 $\mu\text{g/mL}$	8
	34	briaralide H ($R_1 = R_4 = \text{OH}$, $R_2 = \text{OAc}$, $R_3 = \text{H}$)	CC_{50} (Vero, MDCK) = > 100, > 100 $\mu\text{g/mL}$	8

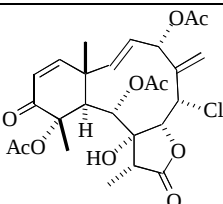
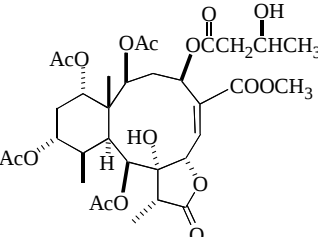
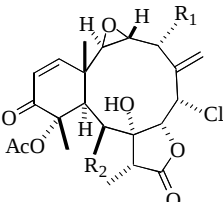
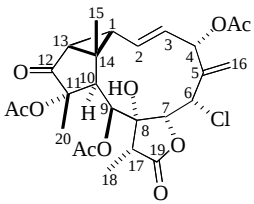
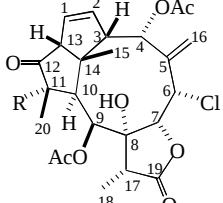
2.2. *Erythropodium* (family Briareidae)

A. *Erythropodium caribaeorum*

In the continuing researches for *E. caribaeorum*, a series of novel briarane-related metabolites, 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, ^1H , 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 auquarian 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*

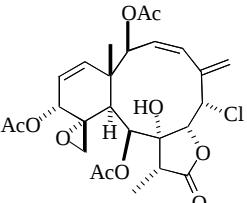
Structure	No.	Name	Ref.
	35	erythrolide R	10
	36	erythrolide S	10
	37	erythrolide T (R ₁ = R ₂ = OAc)	10
	38	erythrolide U (R ₁ = H, R ₂ = OCOCH ₂ OH)	10
	39	erythrolide V	10
	40	aquariolide A (R = OH)	11
	41	aquariolide B (R = OCH ₃)	10
	42	aquariolide C (R = OAc)	10

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, ¹H, and ¹³C 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 $\mu\text{g/mL}$	12
	45	inhibited cytokinesis, causing multinuclei formation on NBT-II cells at 2 $\mu\text{g/mL}$	12
	46		12

2.4. *Junceella* (family Ellisellidae)

A. *Junceella fragilis*

Three new briaranes, 9-*O*-deacetylumbraculolide A (**47**),¹³ junceollolide 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, ¹H, and ¹³C NMR spectrum), particularly in 2D NMR studies. Fragilide A (**49**) is the first briarane derivative possessing a 6-hydroxyl group.¹⁵

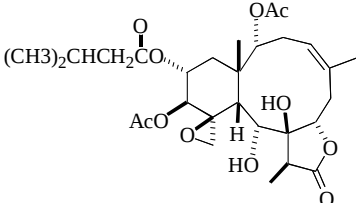
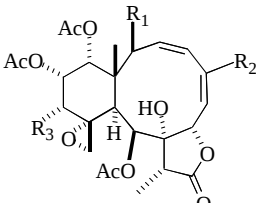
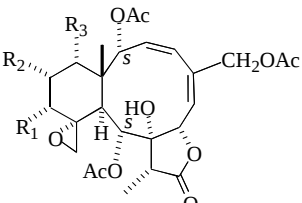
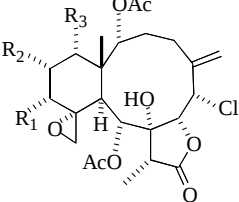
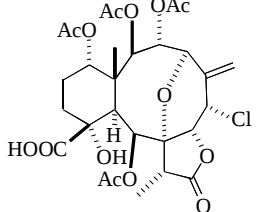
Table 7. The Briarane-Type Metabolites from *J. fragilis*

Structure	No.	Name	Ref.
	47	9- <i>O</i> -deacetylumbraculolide A	13
	48	junceollolide H	14
	49	fragilide A	15

B. *Junceella juncea*

In addition to *J. fragilis*, *J. juncea* 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, ¹H, and ¹³C 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 ₂ OH, R ₃ = H)		18,19
	52	juncenolide C (R ₁ = R ₃ = OAc, R ₂ = CH ₂ OH)	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 ₂ OCH ₃)		19
	54	juncenolide E (R ₁ = OCOCH ₂ CH(CH ₃) ₂ , R ₂ = CH ₂ OH, R ₃ = H)		20
	55	juncin I (R ₁ = R ₃ = OAc, R ₂ = OCOCH ₂ CH(CH ₃) ₂)		21
	56	juncin J (R ₁ = R ₂ = OCOCH ₂ CH(CH ₃) ₂ , R ₃ = OAc)		21
	57	juncin K (R ₁ = R ₃ = OCOCH ₂ CH(CH ₃) ₂ , R ₂ = H)		21
	58	juncin L (R ₁ = R ₂ = OCOCH ₂ CH(CH ₃) ₂ , R ₃ = OAc)		21
	59	juncin M (R ₁ = R ₃ = OCOCH ₂ CH(CH ₃) ₂ , R ₂ = H)		21
	60	juncin N		22

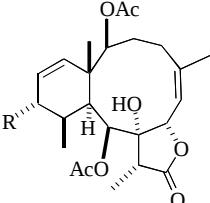
3. PENNATULACEA

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, ¹H and ¹³C NMR spectrum).²³

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

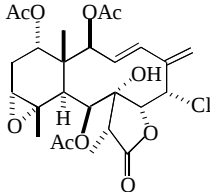
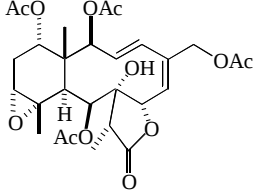
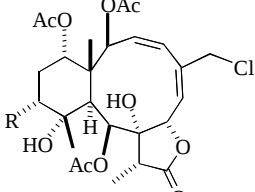
Structure	No.	Name	Ref.
	61	cavernulin A (R = OCO(CH ₂) ₂ CH ₃)	23
	62	cavernulin B (R = OH)	23

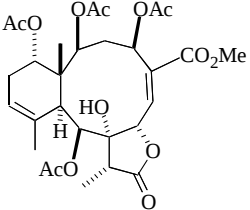
3.2. *Pteroeides* (family Pteroeidae)

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, ¹H, and ¹³C 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 ₂ CH ₃	12

Structure	No.	Name	Ref.
	66		12

ACKNOWLEDGEMENTS

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