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RECENTLY DISCOVERED NATURALLY OCCURRING HETEROCYCLIC ORGANOHALOGEN COMPOUNDS[†]

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Abstract – Amongst the more than 5,000 naturally occurring organohalogen compounds, both biotic and abiotic, are a diverse collection of structurally novel heterocycles. The present review covers this fascinating area of natural products as presented over the past three years.

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[†] Dedicated to Professor Albert Padwa in celebration of his 75th birthday and for his innumerable contributions to heterocyclic chemistry.

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I. INTRODUCTION

The number of known natural organohalogen compounds has grown from 30 in 1968¹ to 200 in 1973² to more than 5,000 today.³⁻⁵ A number of factors account for this extraordinary increase: (1) a revitalization of natural products research in the search for new medicinal compounds, (2) the development of improved isolation, separation, and identification techniques (e.g., SCUBA, remote unmanned submersible vessels, 2D NMR, HRMS), (3) selective bioassays to identify biologically active extracts, and (4) an awareness of folk medicine and ethnobotany for guidance to potentially important organisms.

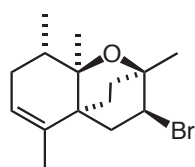
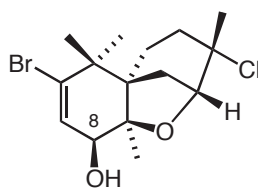
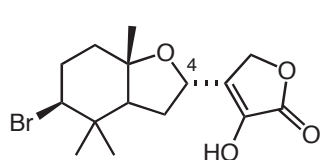
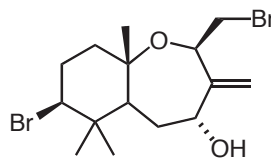
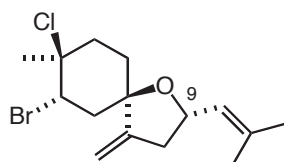
Thus, despite the persistent ignorance of the prevalence of organohalogen in nature,^{6,7} the number of identified natural organohalogen compounds continues to increase. The present review surveys heterocyclic organohalogen natural products reported in the period 2009-2011. As defined by the journal, coverage includes epoxides, lactones, and lactams along with traditional heterocycles.

II. MARINE ORGANISMS

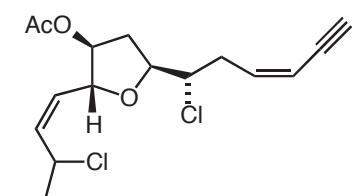
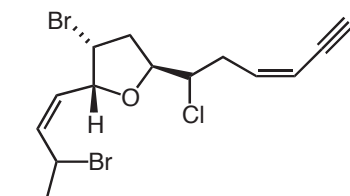
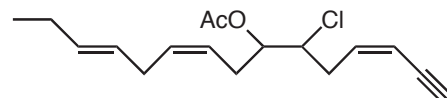
A. Algae

Seaweeds are a rich source of organohalogen compounds,⁸ epitomized by the favorite edible seaweed of native Hawaiians, *Asparagopsis taxiformis* ("limu kohu"), which contains more than 100 organohalogens and is prized for its rich aroma and flavor.^{9,10}

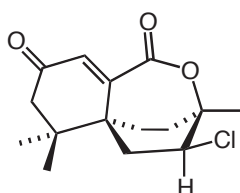
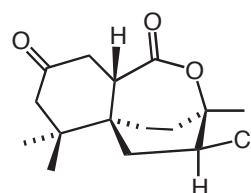
The red algal genus *Laurencia* comprises at least 140 species and continues to yield novel halogenated compounds. *Laurencia composita* from the East China Sea contains the new 2-bromospironippol (**1**) and 10-bromo-3-chloro-2,7-epoxychamigr-9-en-8 β -ol (**2**), along with several known organohalogens.^{11,12} A collection of *Laurencia saitoi* from the Hainan Chinese coast has furnished 2-hydroxyluzofuranone (**3**), 2-hydroxyluzofuranone B (**4**), 4-hydroxypalisadin C (**5**), (9*S*)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (**6**), (9*R*)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (**7**), and 10-bromo-3-chloro-2,7-epoxychamigr-9-en-8 α -ol (**8**), an epimer of **2**.^{13,14}

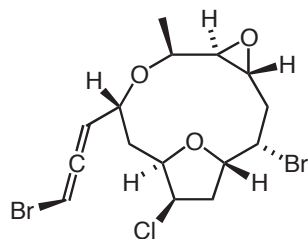
**1** (2-bromospironippol)**2**
8 (C8 epimer)**3** (2-hydroxyluzofuranone)
4 (C4 epimer)**5** (4-hydroxypalisadin C)**6**
7 (C9 epimer)

A sample of *Laurencia glandulifera* from the island of Crete contains five novel halogenated tetrahydrofurans (e.g., **9**, **10**) along with a putative biosynthetic precursor **11**.¹⁵

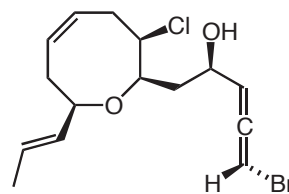
**9****10****11**

The new chamigrenes, gomerolactones A-D, two of which contain chlorine (**12**, **13**), were isolated from *Laurencia majuscula* in the Canary Islands.¹⁶ This site also yielded eight new halogenated acetogenins from a collection of *Laurencia marilzae*, including 12-epoxyobtusallene IV (**14**) and marilzallene (**15**).¹⁷

**12** (gomerolactone C)**13** (gomerolactone D)

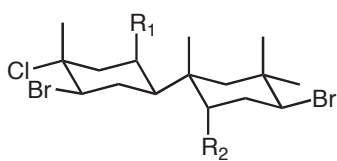
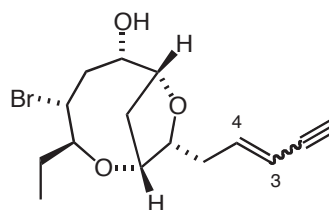


14 (12-epoxyobtusallene IV)

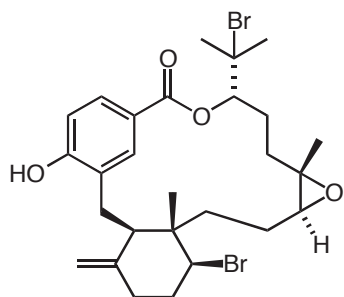


15 (marilzallene)

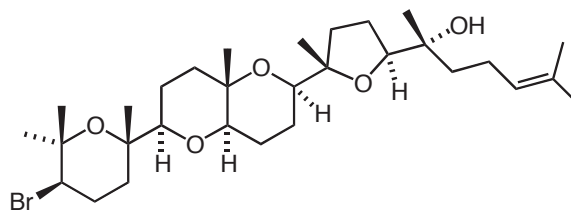
A Brazilian *Laurencia catarinensis* contains seven new related halogenated sesquiterpenes, four of which, (5*S*)-5-acetoxycasptol (**16-19**), are shown.¹⁸ A Philippines sample of *Laurencia* sp. has furnished laurefurenynes A-F, two of which contain bromine (**20**, **21**).¹⁹

((5*S*)-5-acetoxycasptol)16 R₁ = OAc, R₂ = OH17 R₁ = OH, R₂ = OAc18 R₁ = OAc, R₂ = OAc19 R₁ = OAc, R₂ = H20 (laurefurenyne E) $\Delta_{3,4}$ *cis*21 (laurefurenyne F) $\Delta_{3,4}$ *trans*

The Fijian red alga *Callophycus serratus* is a treasure trove of brominated diterpene-benzoate macrolides, the bromophycolides, and 12 new examples were discovered recently, bringing the total to 21.^{20,21} Bromophycolide S (**22**) is shown here.²¹ The Australian red alga *Chondria armata*, a genus closely related to *Laurencia*, has yielded three novel brominated triterpene polyethers, the aplysiols C-E (e.g., **23**), along with several previously known halogenated compounds.²² Noteworthy, this paper revises the relative stereochemistry of aplysiol B.

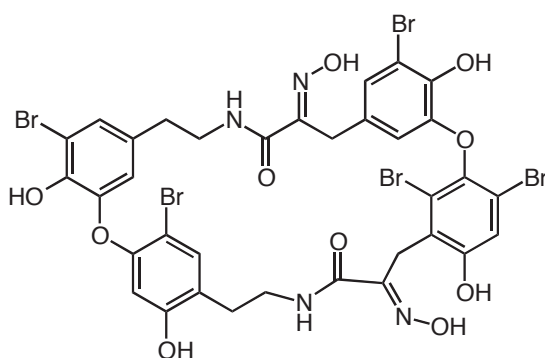


22 (bromophycolide S)

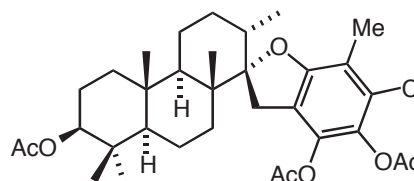


23 (aplysiol C)

The first example of a bastadin-type metabolite to be isolated from a seaweed is lithothamnin A (**24**) from the red alga *Lithothamnion fragilissimum* found in Palau.²³

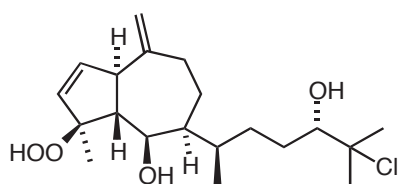


24 (lithothamnin A)

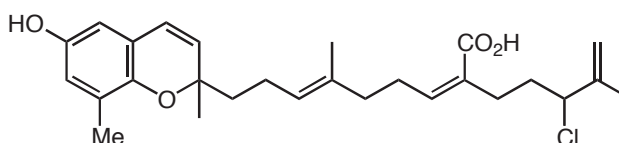


25 (4'-chlorostypotriol triacetate)

The lesser explored brown algae have also yielded novel heterocyclic organohalogens in the past three years. Thus, 4'-chlorostypotriol triacetate (**25**) was identified in *Stypodium flabelliforme* from the Easter Island region (after peracetylation of the extract).²⁴ A Russian population of the brown alga *Dicytota dichotoma* has provided the novel dictyohydroperoxide (**26**),²⁵ and an Australian sample of *Sargassum fallax* contains the unusual meroditerpenoid fallachromenoic acid (**27**).²⁶

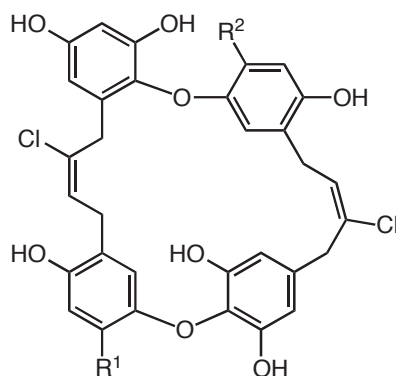


26 (dictyohydroperoxide)



27 (fallachromenoic acid)

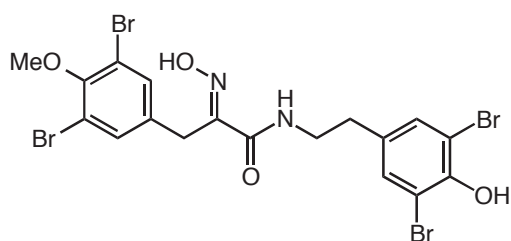
The marine chrysophyte alga *Chrysosphaerum taylori* has yielded eight new antimicrobial chrysosphaentins A-H, four of which are shown here A-D (**28-31**).²⁷ These compounds are vaguely related to the liverwort bazzanins.⁴



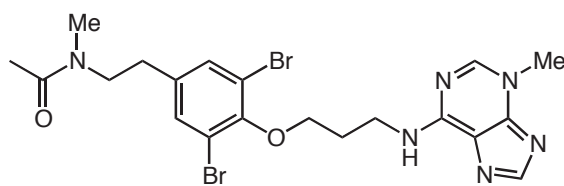
28	R ¹ = Cl	R ² = Cl	(chrysosphaentin A)
29	R ¹ = Br	R ² = Cl	(chrysosphaentin B)
30	R ¹ = Cl	R ² = Br	(chrysosphaentin C)
31	R ¹ = Br	R ² = Br	(chrysosphaentin D)

B. Sponges

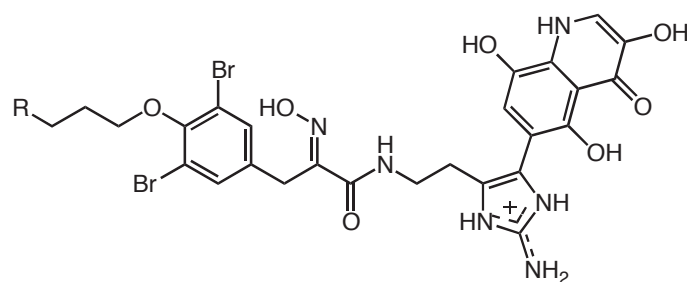
Like marine algae, sponges have long been an amazingly rich source of halogenated metabolites. It is likely that associated bacteria are the origin of at least some of the compounds described herein. Many sponge metabolites are heterocyclic derivatives of bromine-containing tyrosines. New examples include the prototypical (but non-heterocycle) JBIR-44 (**32**) from an Okinawan sponge *Psammaphysilla purpurea*,²⁸ the adenine-substituted aphrocallistin (**33**) from a deep water collection of *Aphrocallistes beatrix* in Florida,²⁹ and tyrokeradines A (**34**) and B (**35**) from an Okinawan Verongida sponge, compounds that contain a novel imidazolyl-quinolone subunit.³⁰



32 (JBIR-44)



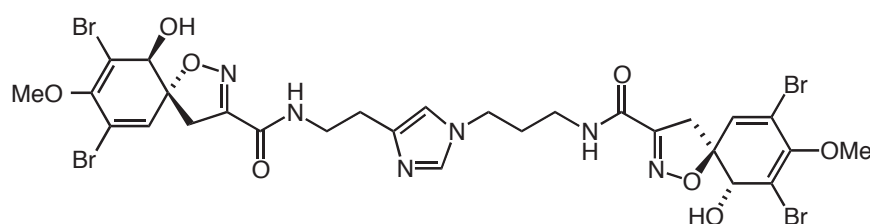
33 (aphrocallistin)



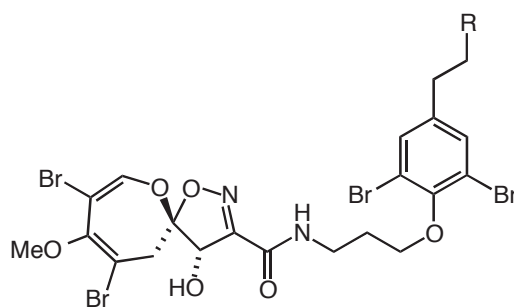
34 (tyrokeradine A) R = Me₃N⁺

35 (tyrokeradine B) R = H₃N⁺

The commonly encountered spirocyclohexadienyl isoxazole moiety is seen with the new sunabedine (**36**) from an Okinawan *Verongida* sponge.³¹ Pseudoceratinazole A (not shown) from the Australian *Pseudoceratina* sp. would appear to be a diastereomer of **36** from the data given.³² The Australian sponge *Hyattella* sp. contains the new antimalarial psammaplysin G (**37**)³³ and psammaplysin F (**38**),³⁴ which is very potent against the malaria parasite, and was isolated along with **37** from an Australian *Pseudoceratina* sp. sponge.³⁴



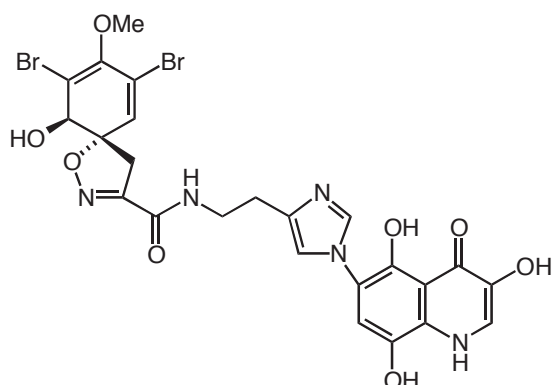
36 (sunabedine)



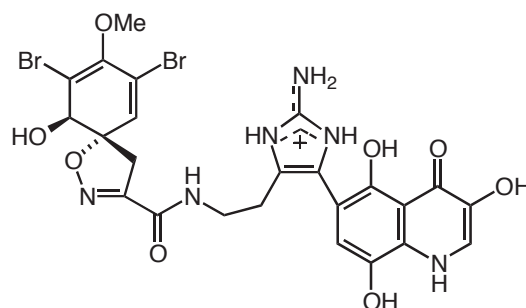
37 (psammaplysin G) R = N(Me)CONH₂

38 (psammaplysin F) R = NMe₃⁺

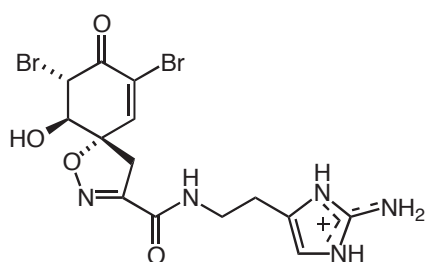
An Okinawan *Pseudoceratina* sp. contains the new ceratinadins A-C (**39-41**),³⁵ and the Australian sponge *Ianthella flabelliformis* has yielded three new bastadins, bastadin 25 (**42**), 15-*O*-sulfonatobastadin 11 (**43**), and bastadin 26 (**44**).³⁶ The related sponge *Ianthella* cf. *reticulata* contains (*E,Z*)-bastadin 19 (not shown), a diastereomer of the known bastadin 19, and the novel dioxepine bastadin 3 (**45**).³⁷



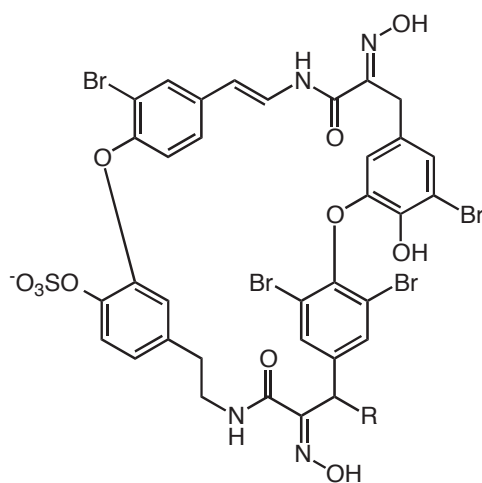
39 (ceratinadin A)



40 (ceratinadin B)

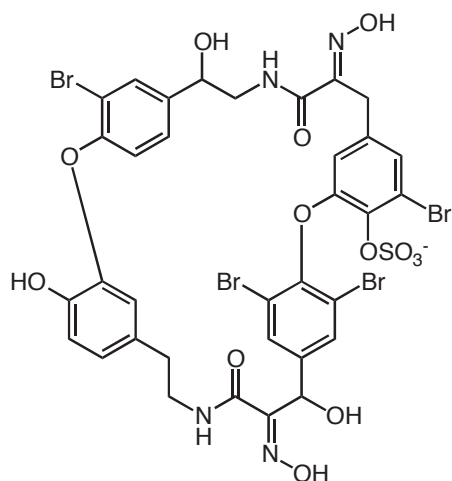


41 (ceratinadin C)

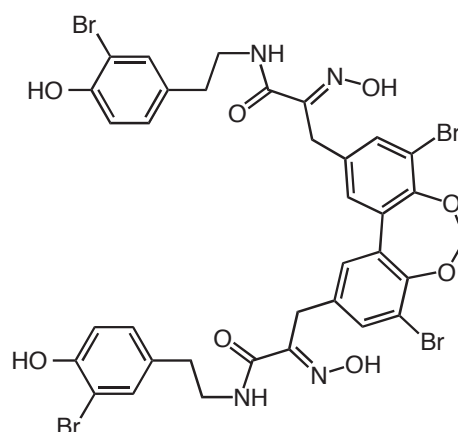


42 R = OH (bastadin 25)

43 R = H (15-O-sulfonatobastadin 11)



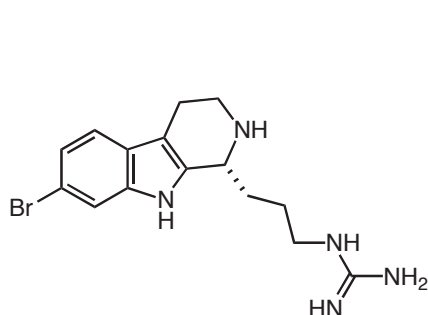
44 (bastadin 26)



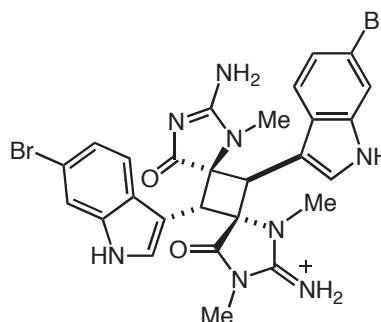
45 (dioxepine bastadin 3)

A dazzling array of new bromotryptophan-derived sponge metabolites was also described over the past three years. The Australian *Ancorina* sp. produces the antimalarial (+)-7-bromotryptargine (**46**),³⁸ and the highly intricate dictazoles A and B (**47**), and the related dictazolines C-E (not shown) were isolated

from a Panamanian sponge *Smenospongia cerebriformis*, all but one of which contain at least one bromine.³⁹

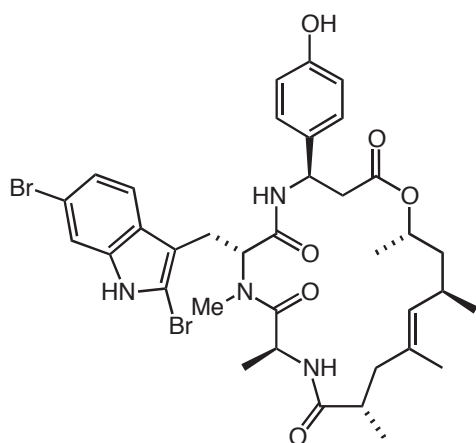


46 ((+)-7-bromotrypargine)

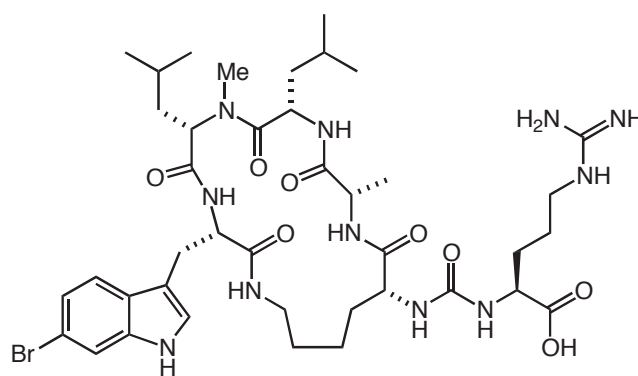


47 (dictazole B)

Seven new analogues of the well-known 2-bromoindole cyclodepsipeptide jaspamide (= jasplakinolide) from the sponge *Jaspis splendens* have been described by three groups.⁴⁰⁻⁴² These include jaspamides M and N,⁴⁰ R,⁴¹ and jasplakinolides Z₃, Z₄, Z₅, and V.⁴² This latter study reports the revision of jasplakinolides R₁ (**48**) (= jaspamide R) and W. Paltolide C (**49**) is a related 6-bromoindole cyclic peptide found in the Palau sponge *Theonella swinhoei*.⁴³

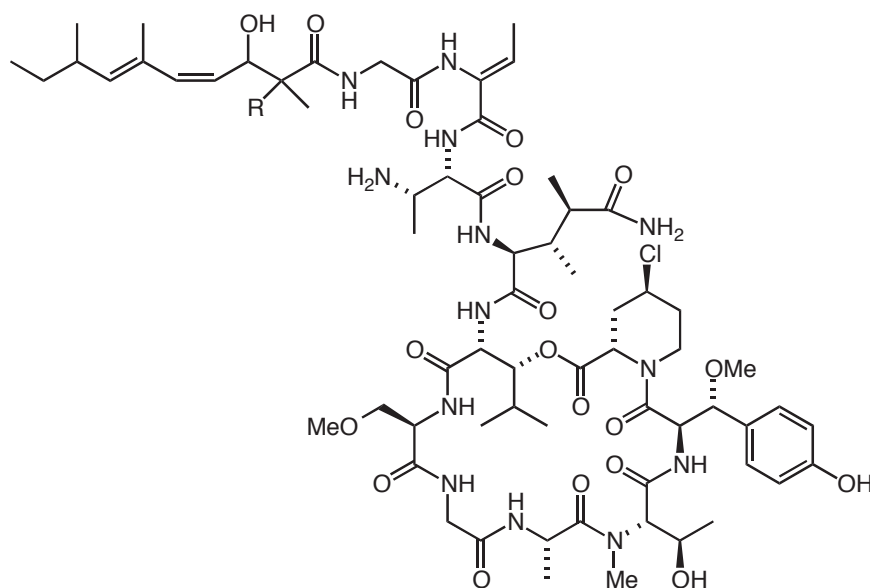


48 (jaspamide R)



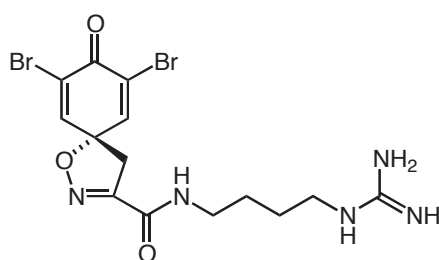
49 (paltolide C)

Four new chlorine-containing cyclic depsipeptides, mirabamides E, F, G (**50**), and H (**51**), were isolated from the Australia Torres Strait sponge *Stelletta clavosa*.⁴⁴ Mirabamides E and F are L-rhamnosyl derivatives of G and H, respectively. The Australian sponge *Suberea clavata* contains clavatadines C (**52**) and D (**53**), novel guanidine alkaloids related to the known purealdin L.⁴⁵

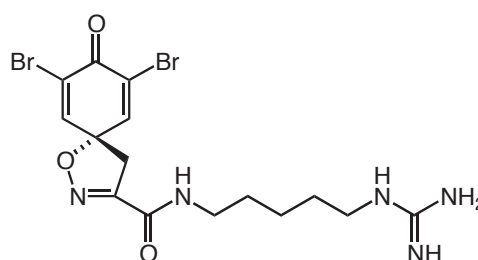


50 (mirabamide G) R = OH

51 (mirabamide H) R = H

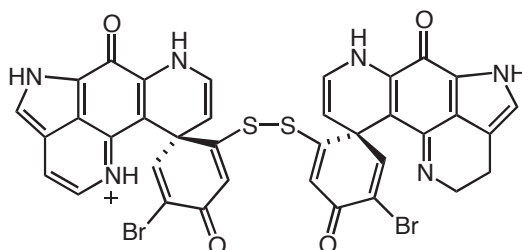


52 (clavatadine C)



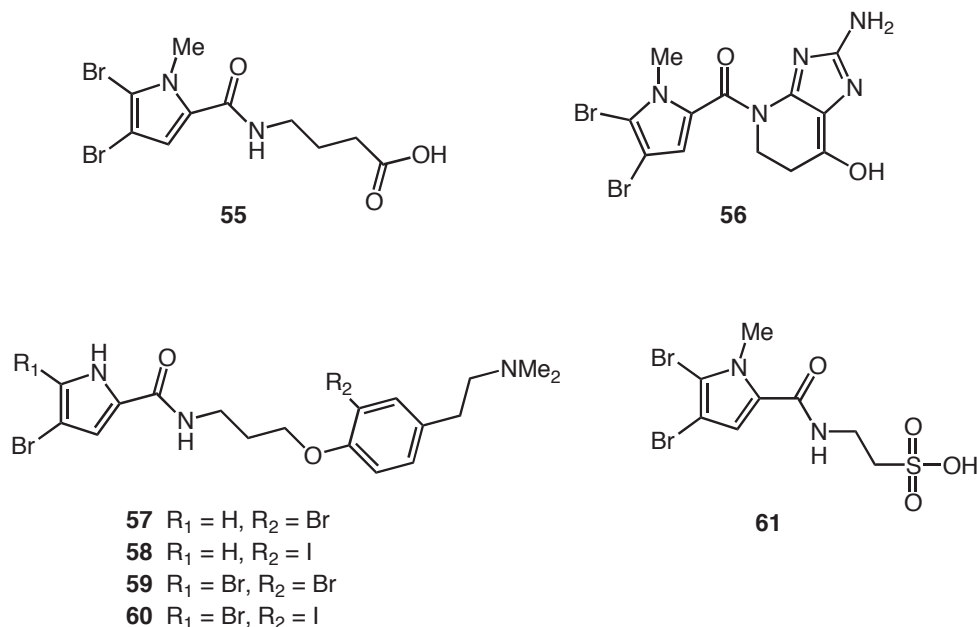
53 (clavatadine D)

New examples of the pyrroloiminoquinone discorhabdins continue to be discovered, four of which contain bromine,⁴⁶⁻⁴⁸ e.g., 16a,17a-dehydrodiscorhabdin W (**54**).⁴⁷

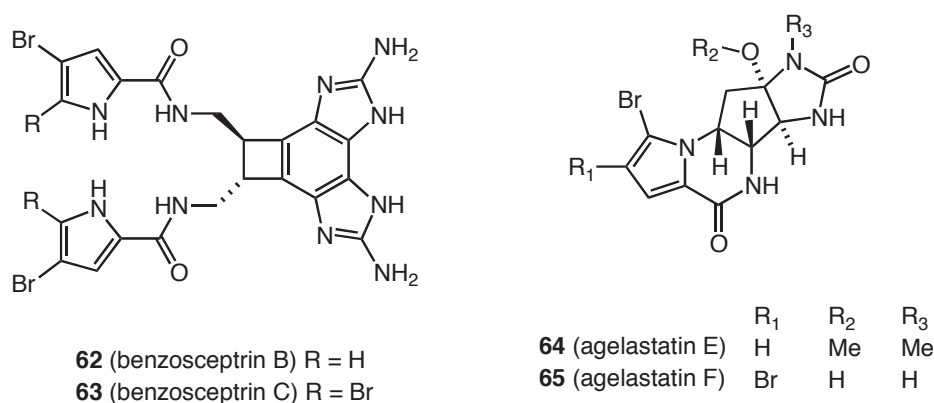


54 (16a,17a-dehydrodiscorhabdin W)

A collection of the recently discovered *Agelas linnaei* from Indonesia has yielded 11 new bromopyrroles (e.g., **55-60**), including the new taurine analogue **61**.⁴⁹

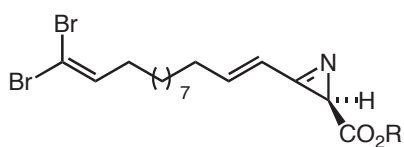


Sponges of the Agelasidae family have also yielded several new dimeric pyrrole-2-aminoimidazole alkaloids, several of which are brominated. Thus, benzoseptrin B (**62**)⁵⁰ and C (**63**)^{51,52} were found in *Agelas cf. mauritiana* (Guadalcanal), *Phakellia* sp. (New Caledonia),⁵⁰ *Agelas dendromorpha* (New Caledonia),⁵¹ and *Agelas* sp. (Okinawa).⁵² In addition, one of these studies uncovered the new agelastatins E (**64**) and F (**65**).⁵¹

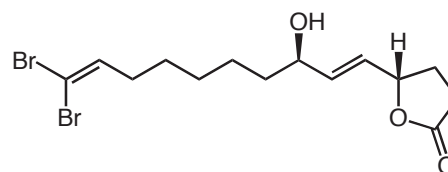


Other examinations of *Agelas* sponges have yielded the bromopyrrole alkaloids nagelamides O and P, mukanadins E and F,⁵³ and nagelamides Q and R,⁵⁴ while a study of *Stylissa carteri* has uncovered the new stylissazoles A-C.⁵⁵ The New Caledonian *Cymbastela cantharella* contains two new dihydrohymenialdisines,⁵⁶ and the acanthamides A-D along with two other new bromopyrrole alkaloids that were identified in *Acanthostylotella* sp.⁵⁷ Unfortunately, space does not permit depicting these metabolites.

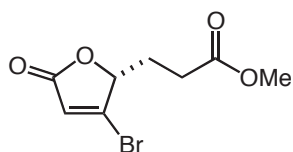
The Fijian sponge *Siliquariaspongia* sp. has afforded a series of bromine-containing motualevic acids, one of which is a heterocycle, motualevic acid F (**66**), along with the corresponding methyl ester (4*E*)-(*R*)-antazirine (**67**).⁵⁸ A Chinese *Xestospongia testudinaria* contains 39 new brominated polyunsaturated lipids, the xestospongienes, several of which are lactones, e.g., xestospongiene A (**68**) and xestospongiene Z₁₂ (**69**), and one is a furan, xestospongiene Z₁₁ (**70**).⁵⁹ The unique polyketide phosphodiester, franklinolides A-C (**71-73**), were isolated from a *Geodia* sp. sponge encrusted with a *Halichondria* sp.⁶⁰



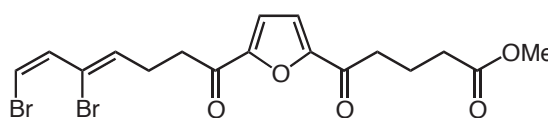
66 (motualevic acid F) R = H
67 ((4*E*)-(*R*)-antazirine) R = Me



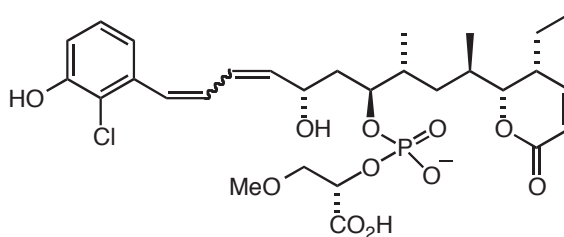
68 (xestospongiene A)



69 (xestospongiene Z₁₂)

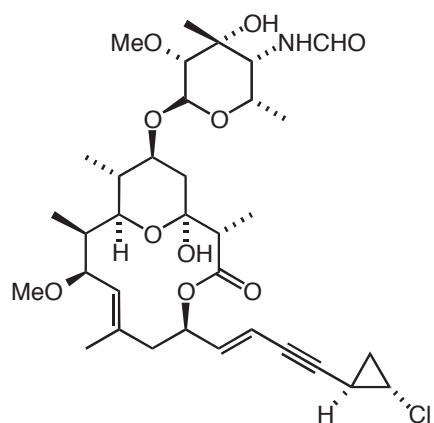


70 (xestospongiene Z₁₁)

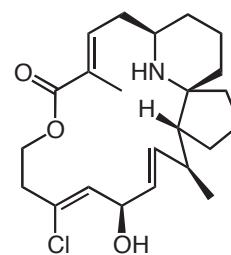


71 12*Z*,14*Z* (franklinolide A)
72 12*E*,14*E* (franklinolide B)
73 12*E*,14*Z* (franklinolide C)

A Western Australia *Phorbas* sp. has produced the new phorbasides G-I (e.g., **74**) in nanogram quantities.⁶¹ The black marine sponge *Halichondria okadai* yielded pinnarine (**75**), a new member of the novel halichlorine family of macrocyclic alkaloids.⁶²



74 (phorbaside I)

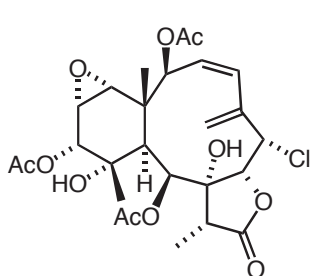


75 (pinnarine)

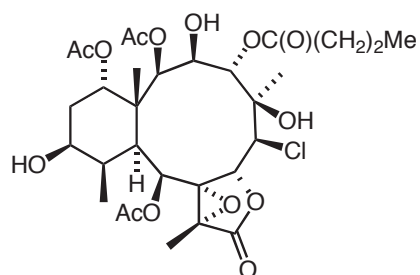
C. Corals

In contrast to marine algae and sponges, gorgonian soft corals generally contain chlorine and not bromine, and typically embedded in a dazzling array of briarane diterpenoids.

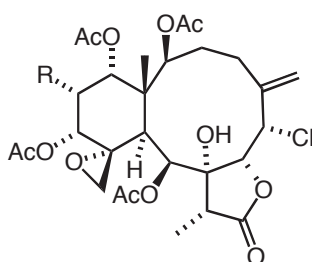
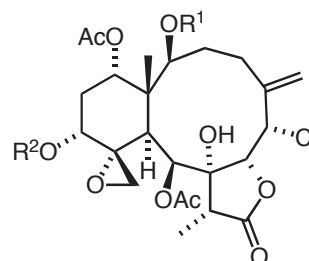
Recent examples include briaexcavatin U (**76**)⁶³ and excavatoid P (**77**)⁶⁴ from the cultured octocoral *Briareum excavatum*, and juncin ZII (**78**)⁶⁵ and juncenolides H-J (**79-81**)⁶⁶ from *Junceella juncea* living in the South China Sea.



76 (briaexcavatin U)

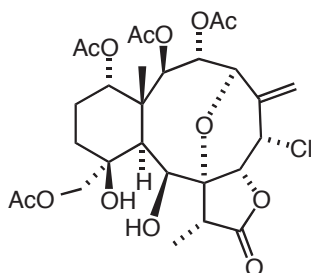
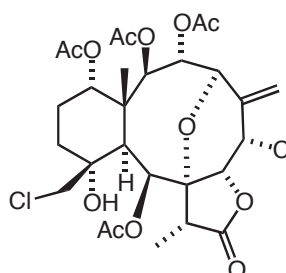
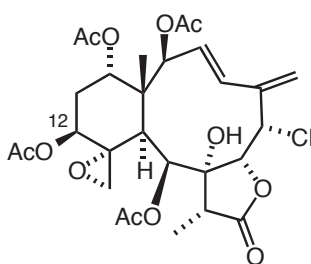
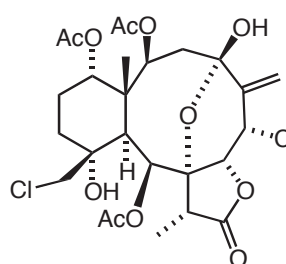
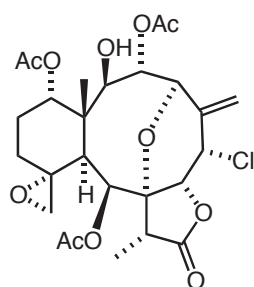
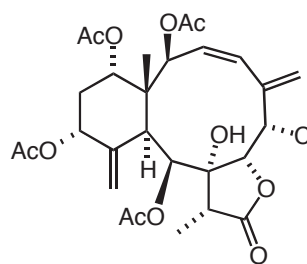
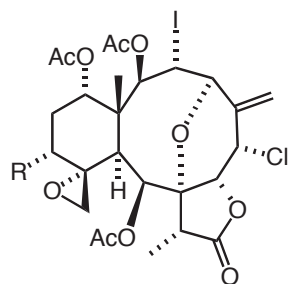
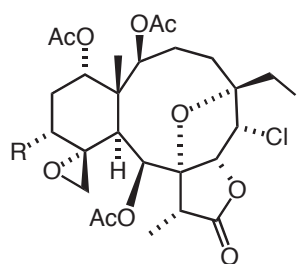


77 (excavatoid P)

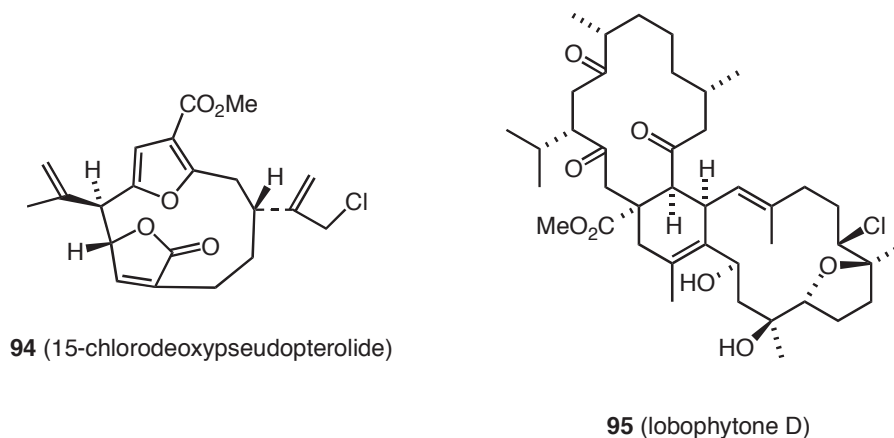
78 (juncin ZII) R = OCO(CH₂)₂CHMe₂

79 (juncenolide H) R¹ = R² = Ac
 80 (juncenolide I) R¹ = Me₂CHOO, R² = Ac
 81 (juncenolide J) R¹ = Ac, R² = Me₂CHCH₂CO

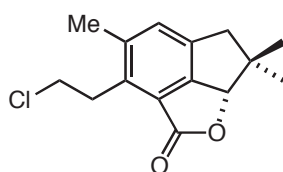
The gorgonian *Junceella fragilis* continues to be the source of numerous new briaranes, such as the chlorine containing fragilides E (**82**),⁶⁷ F (**83**),⁶⁸ G (**84**),⁶⁸ 12-*epi*-G (**85**),⁶⁹ H (**86**),⁷⁰ J (**87**),⁷¹ and robustolide L (**88**).⁷¹ The first iodine-containing briaranes to be found in nature are the dichotellides A-E (**89-93**) from *Dichotella gemmacea*.⁷²

**82** (fragilide E)**83** (fragilide F)**84** (fragilide G)**85** (12- α -OAc)**86** (fragilide H)**87** (fragilide J)**88** (robustolide L)**89** (dichotellide A) R = OC(O)CH₂CHMe₂**90** (dichotellide B) R = OAc**91** (dichotellide C) R = H**92** (dichotellide D) R = OC(O)CH₂CHMe₂**93** (dichotellide E) R = OAc

The novel 15-chlorodeoxypseudopterolide (**94**), the first halogenated pseudopterane diterpene to be discovered, was isolated from the Bahamian octocoral *Pseudopterogorgia acerosa*.⁷³ Whereas **94** displays activity against the HCT116 cell line, the nonchlorinated derivative is inactive. The soft coral *Lobophytum pauciflorum* contains seven biscebranoids, one of which, lobophytone D (**95**), is chlorinated.⁷⁴



Interestingly, only **95** of this series is active in inhibiting inducible nitric oxide synthase. The Antarctic soft coral *Alcyonium grandis* has yielded six chlorine-containing sesquiterpenoids, but only **96** is a heterocycle.⁷⁵

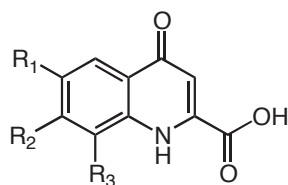


96 (alcyoterosin P)

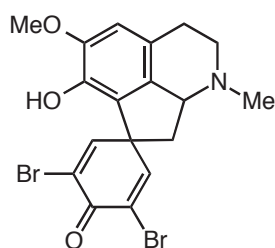
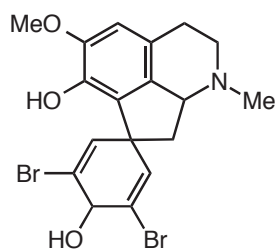
D. Tunicates

Tunicates (= ascidians) (class Ascidiacea) are a rich and diverse source of halogenated metabolites, most of which are bromine-containing heterocycles.

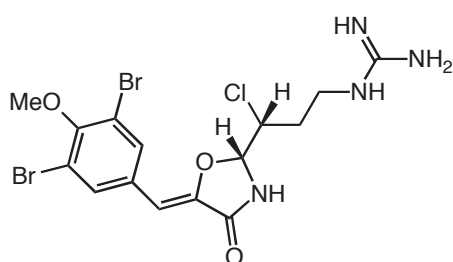
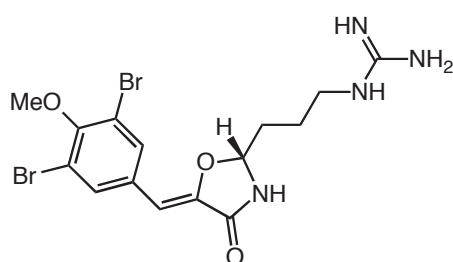
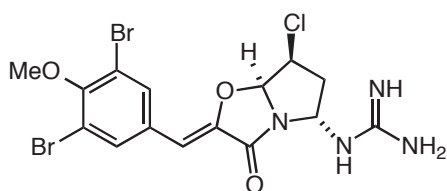
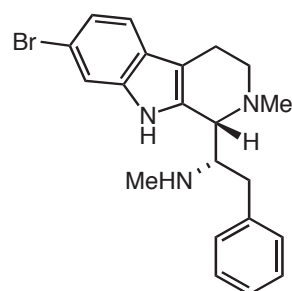
The Australian ascidian *Aplidium caelestis* produces the novel quinolone carboxylic acids, caelestines A-D (**97-100**), a previously unknown class of natural organohalogenes.⁷⁶ An unidentified Madagascan tunicate has yielded the first marine proaporphine alkaloids, saldedines A (**101**) and B (**102**).⁷⁷

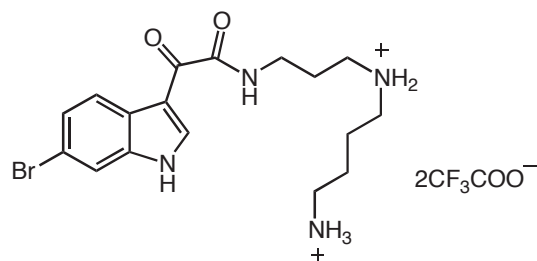


- 97** (caelestine A) $R_1 = H, R_2 = Br, R_3 = H$
98 (caelestine B) $R_1 = Br, R_2 = Br, R_3 = H$
99 (caelestine C) $R_1 = Br, R_2 = H, R_3 = OMe$
100 (caelestine D) $R_1 = Br, R_2 = Br, R_3 = OMe$

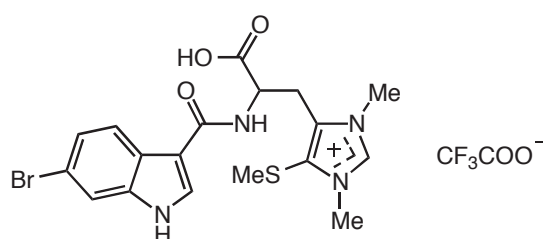
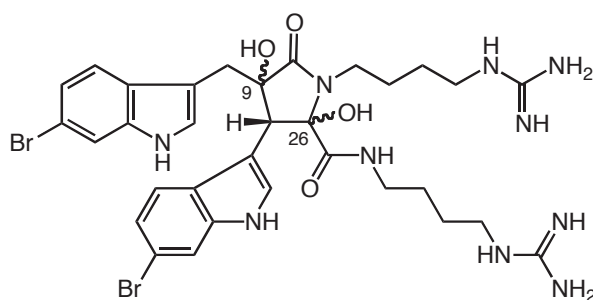
**101** (saldedine A)**102** (saldedine B)

The sub-arctic ascidian *Synoicum pulmonaria* from the coast of Norway has yielded synoxazolidinones A-C (**103-105**), marine metabolites containing the rare 4-oxazolidinone in nature.^{78,79} Tunicates of the genus *Eudistoma* continue to afford brominated β -carboline alkaloids, and a recent example is eudistomidin G (**106**) from the Okinawan *Eudistoma glaucus*.⁸⁰ The New Zealand ascidian *Didemnum* sp., also a rich repository of bromine-containing alkaloids, has yielded didemnidine B (**107**) along with the non-brominated didemnidine A.⁸¹

**103** (synoxazolidinone A)**104** (synoxazolidinone B)**105** (synoxazolidinone C)**106** (eudistomidin G)

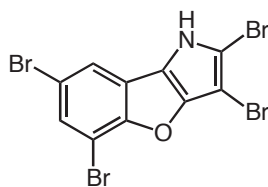
**107** (didemnidine B)

Leptoclinidamine C (**108**) was identified in the Australian ascidian *Leptoclinides durus* and this novel bromoindole alkaloid contains the rare 5-(methylthio)histidine unit.⁸² An ascidian from the Great Barrier Reef, *Eusynstyela latericus*, has furnished the three dimeric 6-bromoindole metabolites eusynstyelamides A-C (**109-111**).⁸³

**108** (leptoclinidamine C)**109** (eusynstyelamide A) (9 α OH, 26 β OH)**110** (eusynstyelamide B) (9 α OH, 26 α OH)**111** (eusynstyelamide C) (9 β OH, 26 α OH)

E. Nudibranchs

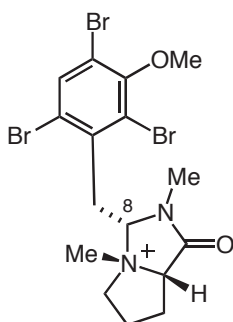
Only one heterocyclic organohalogen was reported from a nudibranch in this three year time frame. The novel benzofuro[3,2-*b*]pyrrole **112** was actually isolated from a *Pseudoalteromonas* sp. on the surface of an unidentified nudibranch collected in Oahu.⁸⁴



112

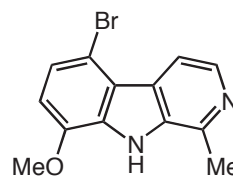
F. Bryozoans

The Australian bryozoan *Amathia wilsoni* contains the novel wilsoniamines A (**113**) and B (**114**), which possess the hexahydropyrrolo[1,2-*c*]imidazol-1-one ring system, unprecedented in nature.⁸⁵ The New Zealand *Pterocella vesiculosa* has yielded the new β -carboline alkaloid **115**.⁸⁶ The prolific *Flustra foliacea* continues to exhibit its synthetic virtuosity and a collection of this animal from Scandinavia and Canada has yielded nine new brominated flustramine alkaloids, **116-124**.⁸⁷ Two related dimers (not shown) may be isolation artifacts.

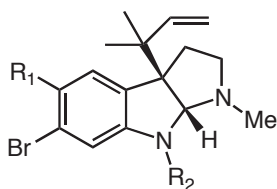
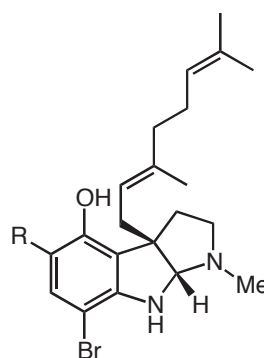


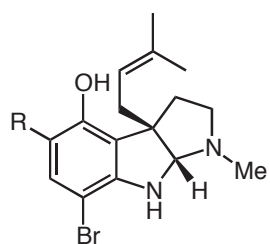
113 (wilsoniamine A)

114 (wilsoniamine B) (C-8 epimer)

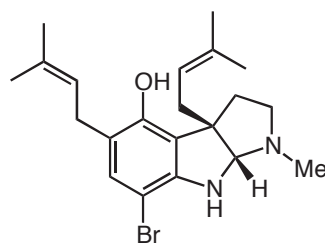


115

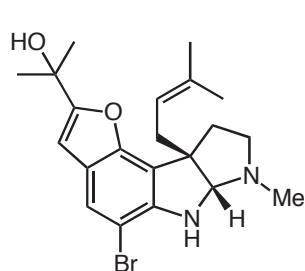
116 (flustramine F) $R_1 = H, R_2 = Ac$ 117 (flustramine G) $R_1 = Br, R_2 = H$ 118 (flustramine H) $R = H$ 119 (flustramine J) $R = Br$



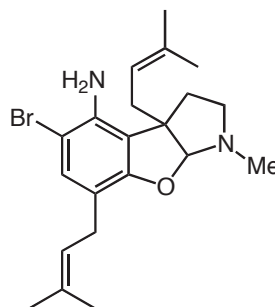
120 (flustramine I) R = H
121 (flustramine K) R = Br



122 (flustramine L)

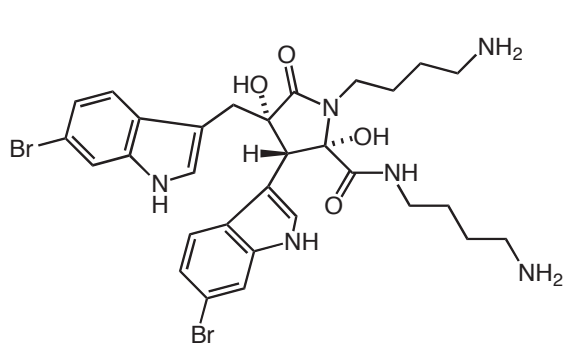


123 (flustramine M)

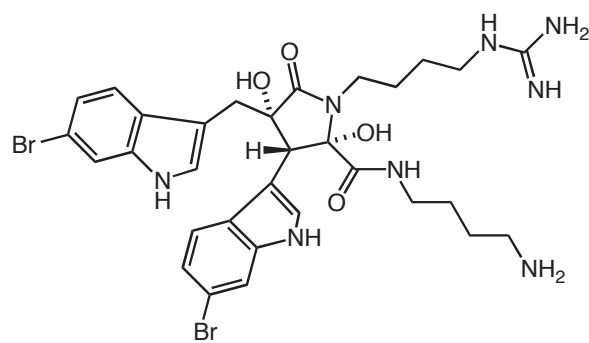


124 (flustramine N)

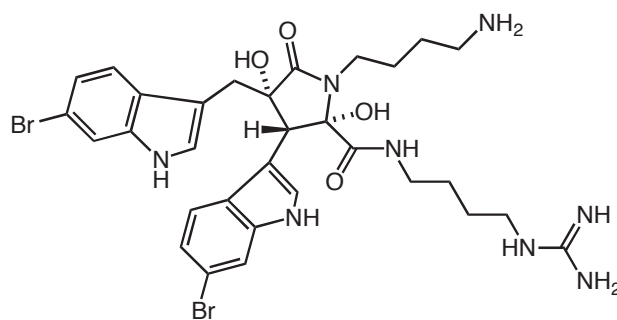
The Arctic bryozoan *Tegella cf. spitzbergensis* has afforded the new eusynstyelamides D-F (**125-127**), in addition to the enantiomer (not shown) of eusynstyelamide B (**110**).⁸⁸



125 (eusynstyelamide D)



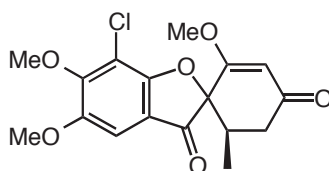
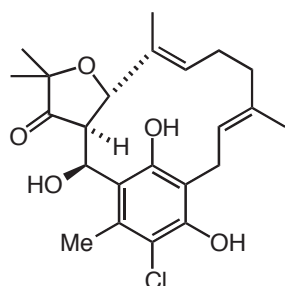
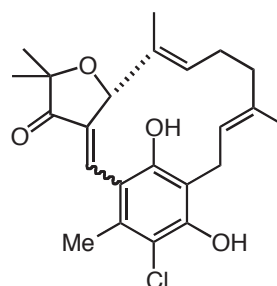
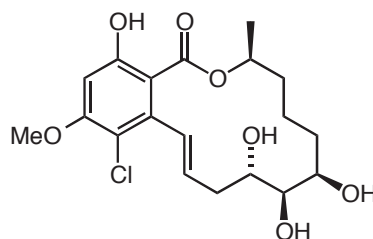
126 (eusynstyelamide E)



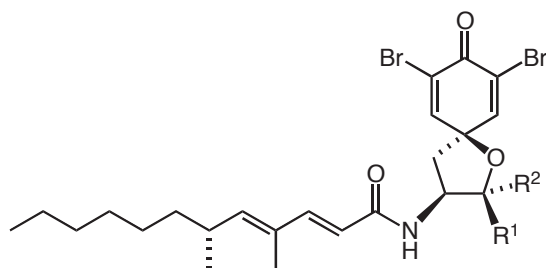
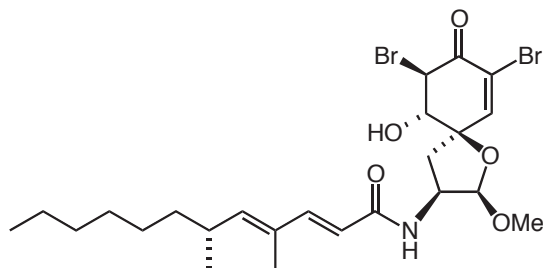
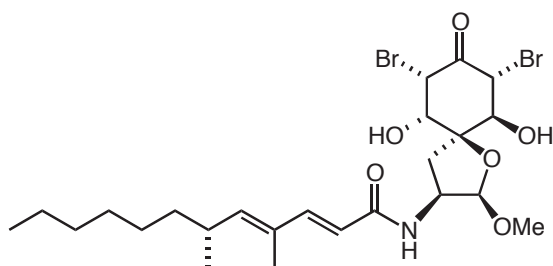
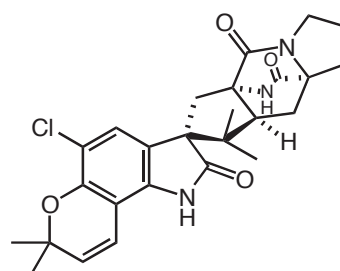
127 (eusynstyelamide F)

G. Fungi

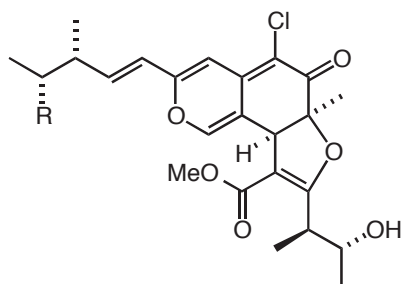
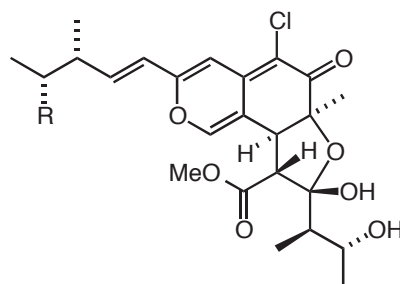
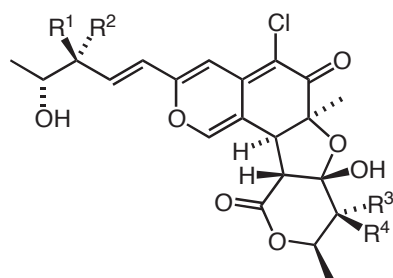
Although not found in a marine fungus, one of the first halogenated natural products to be identified was griseofulvin in *Penicillium griseo-fulvum*. A new derivative of this fungal metabolite is **128**, isolated from the marine mangrove fungus *Sporothrix* sp. from the South China Sea coast.⁸⁹ The marine fungus *Acremonium* sp. found living on a *Stelletta* sp. sponge on the Korean coast produces the sesquiterpenoids acremofuranone A (**129**) and B (**130**), along with several non-heterocyclic chlorinated analogues.⁹⁰ One of three new cochliomycins, cochliomycin C (**131**), was isolated from a gorgonian (*Dichotella gemmacea*)-derived fungus *Cochliobolus lunatus* collected in the South China Sea. These novel resorcylic acid lactones display activity against larval settlement of the barnacle *Balanus amphitrite*.⁹¹

**128****129** (acremofuranone A)**130** (acremofuranone B)**131** (cochliomycin C)

The sponge *Halichondria japonica*-derived fungus *Gymnascella dankaliensis* has afforded four new gymnastatins I-K (**132-135**) when the culture medium contains bromide.⁹² The novel notoamide N (**136**) was isolated from a marine *Aspergillus* sp. fungus, the only one of 16 related new metabolites from this organism to contain chlorine.⁹³

**132** (gymnastatin I) $R^1 = OH$, $R^2 = H$ **133** (gymnastatin I) $R^1 = H$, $R^2 = OH$ **134** (gymnastatin J)**135** (gymnastatin K)**136** (notoamide N)

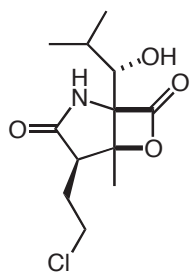
The fungus *Chaetomium globosum* that was originally isolated from the marine fish *Mugil cephalus* has yielded a large number of cytotoxic metabolites designated as chaetomugilins. New examples include chaetomugilins G (**137**),⁹⁴ H (**138**),⁹⁴ *seco*-A (**139**),⁹⁵ *seco*-D (**140**),⁹⁵ 11-*epi*-A (**141**),⁹⁶ and 4'-*epi*-A (**142**).⁹⁶

**137** (chaetomugilin G) $R = OH$ **138** (chaetomugilin H) $R = H$ **139** (*seco*-chaetomugilin A) $R = OH$ **140** (*seco*-chaetomugilin D) $R = H$ **141** (11-*epi*chaetomugilin A)**142** (4'-*epi*chaetomugilin A)

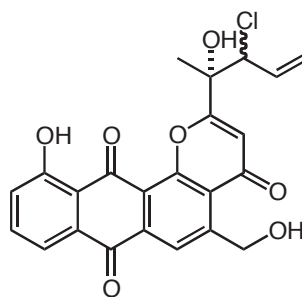
	R^1	R^2	R^3	R^4
141 (11- <i>epi</i> chaetomugilin A)	Me	H	Me	H
142 (4'- <i>epi</i> chaetomugilin A)	H	Me	H	Me

H. Bacteria

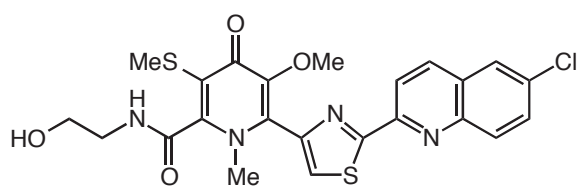
Like the study of marine fungi, the exploration of marine bacteria has intensified in recent years,⁹⁷ and one notable member of this class, salinosporamide A (NPI-0052), has advanced into human clinical trials as an anticancer agent.⁹⁸ The organism that produces salinosporamide A, *Salinispora tropica*, has also afforded antiprotealide (**143**),⁹⁹ while the related marine sediment bacterium, *Salinispora arenicola*, from Palau produces the chlorohydrin saliniquinone C (**144**), which is related to the pluramycin-altromycin class of metabolites.¹⁰⁰ Saliniquinone A (not chlorinated) displays potent inhibition of the human colon HCT-116 cell line (IC_{50} 9.9×10^{-9} M). A marine *Saccharomonospora* sp. from a La Jolla California sediment has yielded the novel alkaloid iodopyridone (**145**), which is also active against the HCT-116 cell line.¹⁰¹ The marine bacterium *Thermovibrio ammonificans* living on a deep-sea hydrothermal vent chimney on the East Pacific Rise yielded its first identified secondary metabolites, ammonificins A (**146**) and B (**147**).¹⁰²



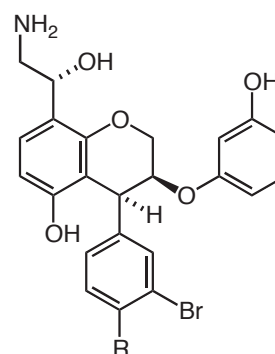
143 (antiprotealide)



144 (saliniquinone C)



145 (iodopyridone)

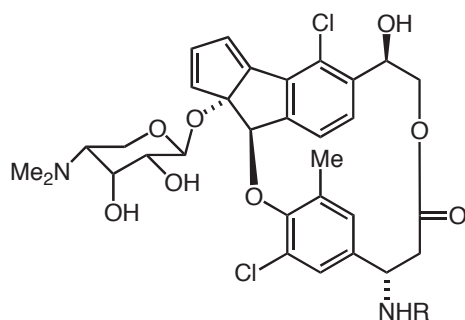


146 (ammonificin A) R = OH

147 (ammonificin B) R = Br

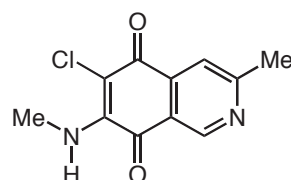
A marine-derived sediment bacterium from Fiji, *Nocardiosis* sp., has afforded fijiolides A (**148**) and B (**149**).¹⁰³ These inhibitors of NF- κ B activation possess a chlorocyclopenta[*a*]indene ring system similar to that found in the sporolides and cyanosporasides. Marine *Streptomyces* species are a rich source of unique halogenated metabolites, including mansouramycin B (**150**) isolated from a sediment collected on

the North Coast of Germany,¹⁰⁴ ammosamides A (**151**) and B (**152**) from a Bahaman bottom sediment,¹⁰⁵ and JBIR-34 (**153**) and JBIR-35 (**154**) from a sponge (*Haliclona* sp.)-derived *Streptomyces* from Japan.¹⁰⁶ Both ammosamides A and B show significant in vitro cytotoxicity against HCT-116 ($IC_{50} = 0.32 \mu M$).¹⁰⁵

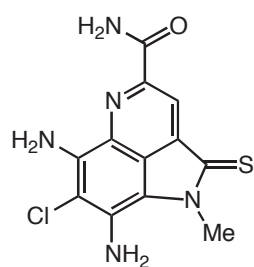


148 (fijiolide A), R = COMe

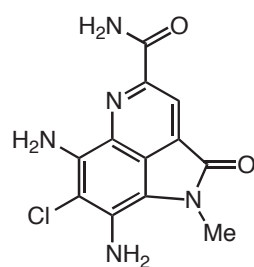
149 (fijiolide B), R = H



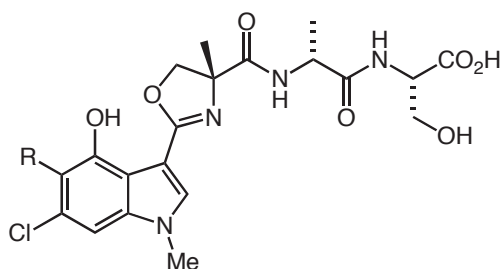
150 (mansouramycin B)



151 (ammosamide A)



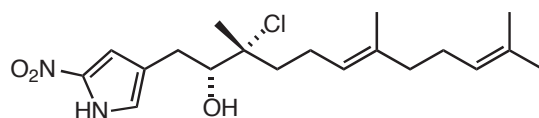
152 (ammosamide B)



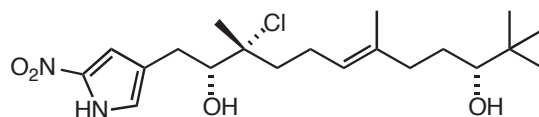
153 (JBIR-34) R = Me

154 (JBIR-35) R = H

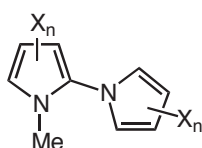
The novel nitropyrrolins A-E were isolated from a marine-derived bacterium of the *Streptomycetaceae* family, and two of these metabolites, C (**155**) and E (**156**), are chlorohydrins.¹⁰⁷ Although the source of the growing collection of polyhalogenated 1'-methyl-1,2'-bipyrroles (**157**) has yet to be established, their environmental ubiquity is expanding to being found in various marine mammals¹⁰⁸ and in the liver of the tiger shark (*Galeocercus cuvier*).¹⁰⁹ Most likely these unusual halogenated bipyrroles are the product of marine bacteria.



155 (nitropyrrolin C)

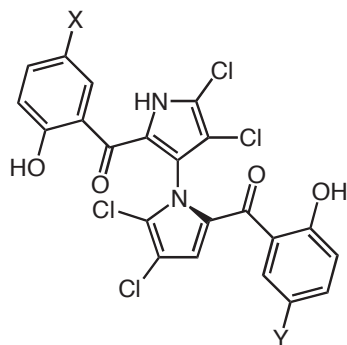


156 (nitropyrrolin E)



157 X = Cl, Br, H

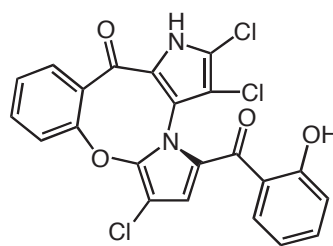
A La Jolla deep ocean sediment has yielded what is probably a new *Streptomyces* species, which produces the novel bipyrrolic marinopyrroles A-F.¹¹⁰ New examples of these remarkable compounds reported in 2010 include marinopyrroles C (**158**), D (**159**), E (**160**) and F (**161**),¹¹¹ which, except for F (**161**), exist as optically active atropoenantiomers, similar to that observed for 5,5'-dichloro-1,1'-dimethyl-3,3',4,4'-tetrabromo-2,2'-bipyrrrole.¹¹² The marinopyrroles display excellent activity against methicillin-resistant *Staphylococcus aureus* bacteria.^{110,111} The marine dinoflagellate *Karlodinium veneficum* produces several powerfully toxic ichthyotoxins, including karlotoxin 2 (= KmTx 2) (**162**),¹¹³ 65-*E*-chloro-KmTx 1 (**163**),¹¹⁴ and 64-*E*-chloro-KmTx 3 (**164**).¹¹⁴ These compounds are responsible for massive fish kills and significant economic loss to the seafood industry.



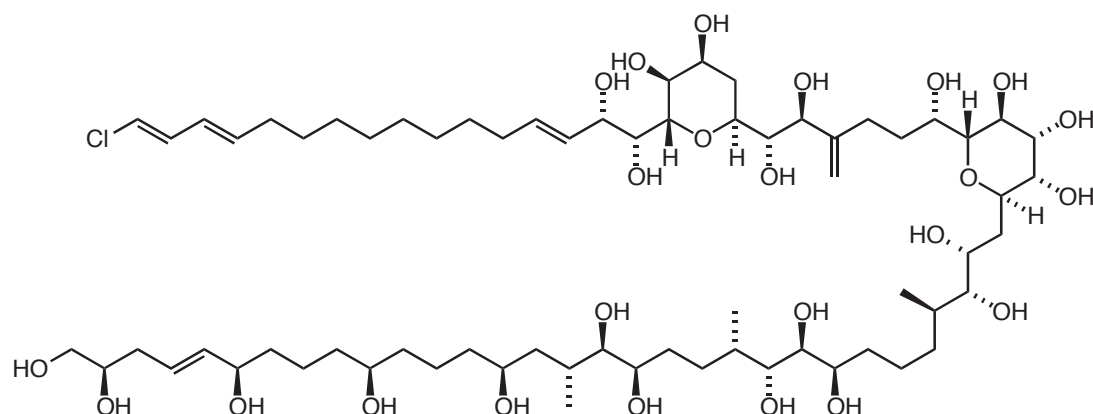
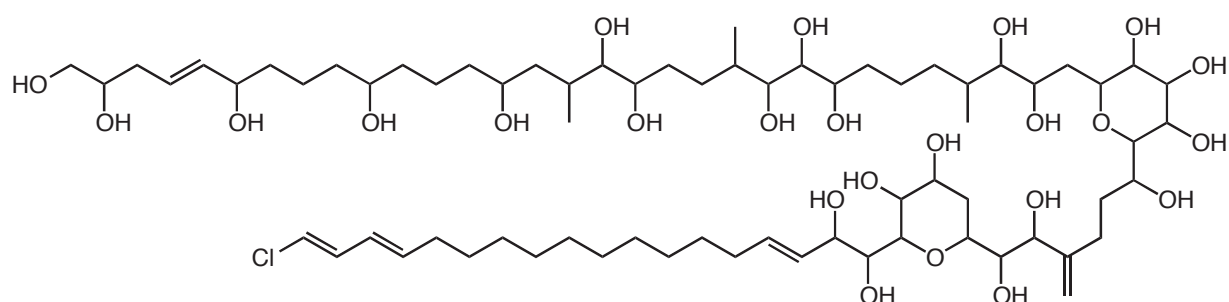
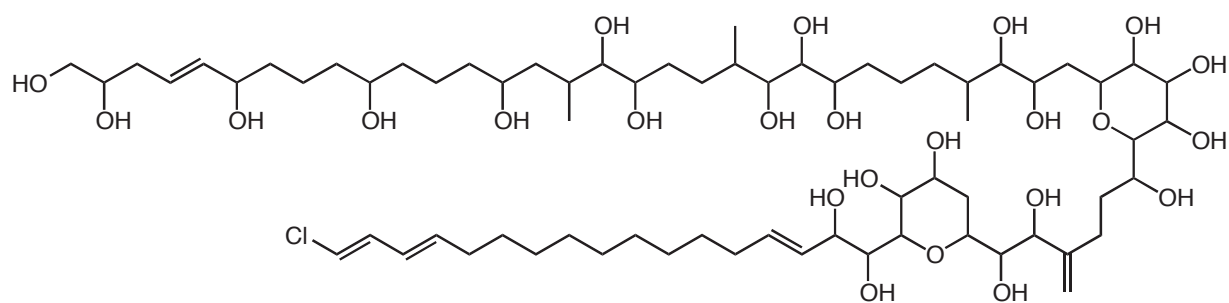
158 (marinopyrrole C) X = Cl, Y = H

159 (marinopyrrole D) X = H, Y = Cl

160 (marinopyrrole E) X = H, Y = Br

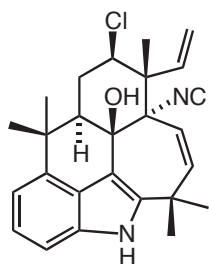


161 (marinopyrrole F)

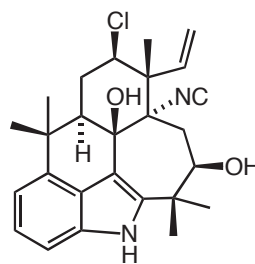
**162** (karlotoxin 2) (KmTx2)**163****164**

I. Cyanobacteria

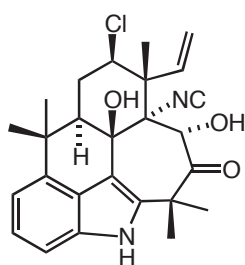
More than 1,000 natural products have been identified in cyanobacteria (blue-green algae),¹¹⁵ many of which contain halogen, usually chlorine. Three new chlorinated ambigueine K, M, and O isonitriles (**165-167**) were isolated from cultured *Fischerella ambigua*.¹¹⁵ Both **165** and **166** show potent activity against *Mycobacterium tuberculosis* and *Bacillus anthracis*. Further study of this same cyanobacterium characterized the new fischambigueine B (**168**) along with related non-chlorinated analogues.¹¹⁶



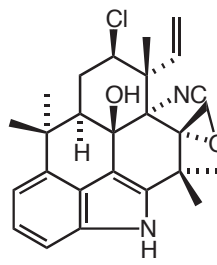
165 (ambiguine K isonitrile)



166 (ambiguine M isonitrile)

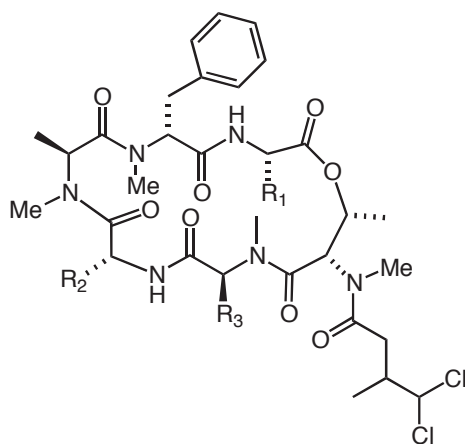


167 (ambiguine O isonitrile)

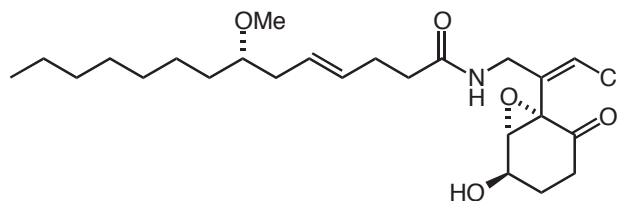
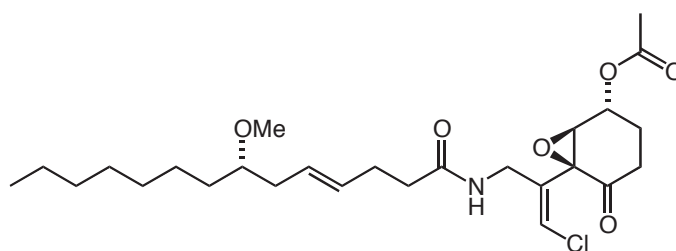


168 (fischambiguine B)

The cyanobacteria genus *Lyngbya* is an amazing source of novel metabolites, including many chlorine-containing compounds. Leading the genus is *Lyngbya majuscula*, and a recent study of this alga from Grenada has identified four new organochlorines, two of which, itralamides A (**169**) and B (**170**), are depsipeptides.¹¹⁷ A Floridian sample of this cyanobacterium has afforded the new 8-*epi*-malyngamide C (**171**), the latest in a series of about 30 known malyngamides, most of which do not contain a heterocyclic ring.¹¹⁸ A related epoxide-containing metabolite is 8-*O*-acetyl-8-*epi*-malyngamide C (**172**) that was found in a Grenada collection of *Lyngbya majuscula*.¹¹⁹ This investigation also identified **171** in the cyanobacterium.

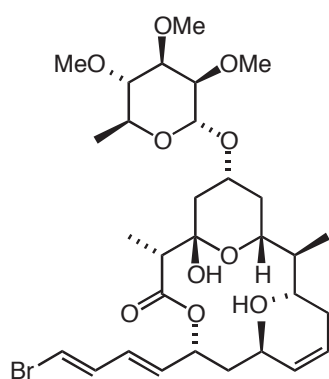
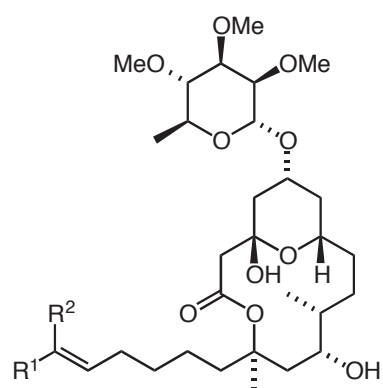


169 (itralamide A) $R_1 = \text{Me}$, $R_2 = \text{Me}$, $R_3 = i\text{-Pr}$
170 (itralamide B) $R_1 = i\text{-Pr}$, $R_2 = i\text{-Pr}$, $R_3 = \text{Me}$

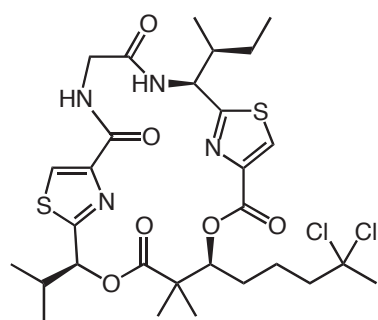
171 (8-*epi*-malyngamide C)

172

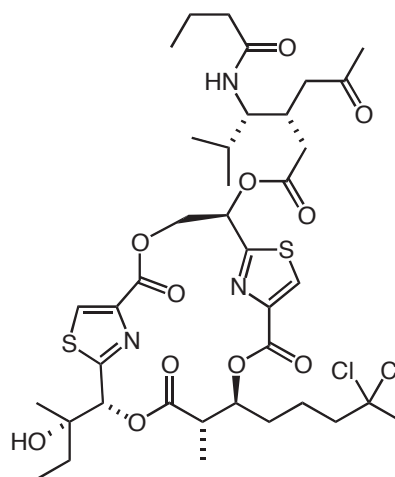
A study of *Lyngbya bouillonii* from Guam has discovered six new organochlorine and organobromine metabolites, 2-*epi*-lyngbyaloside (**173**), 18*E*- (**174**) and 18*Z*-lyngbyaloside C (**175**), 27-deoxylyngbyabellin A (**176**), lyngbyabellin J (**177**), and laingolide B (**178**), along with several related previously known compounds.¹²⁰ A separate study of this Guamanian cyanobacterium discovered bouillomide B (**179**).¹²¹

173 (2-*epi*-lyngbyaloside)

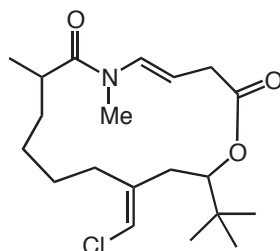
	R ¹	R ²
174 (18 <i>E</i> -lyngbyaloside C)	Br	H
175 (18 <i>Z</i> -lyngbyaloside C)	H	Br



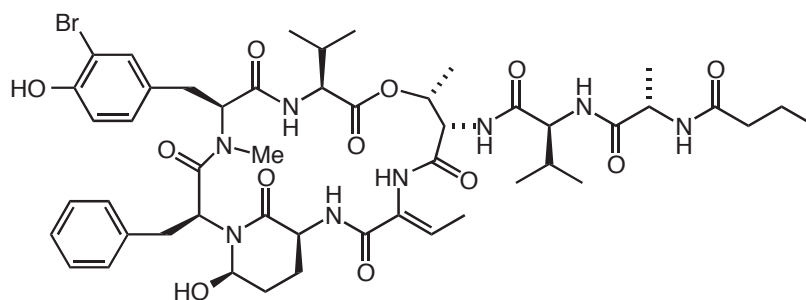
176 (27-deoxylyngbyabellin A)



177 (lyngbyabellin J)

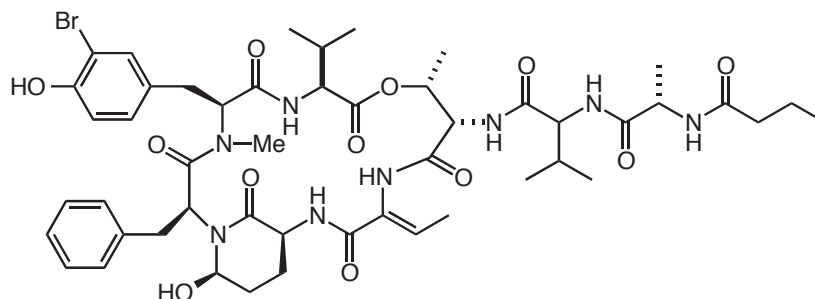
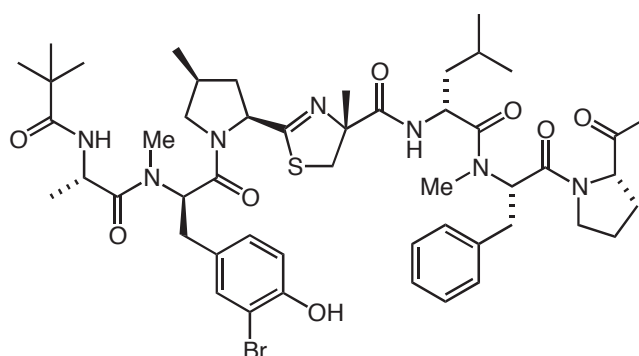


178 (laingolide B)

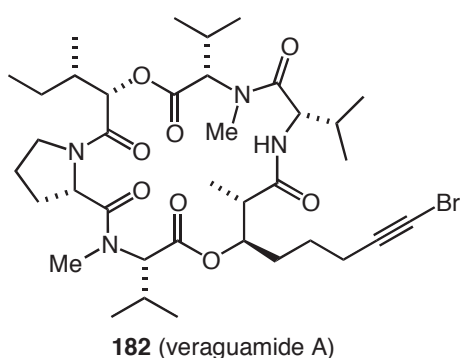
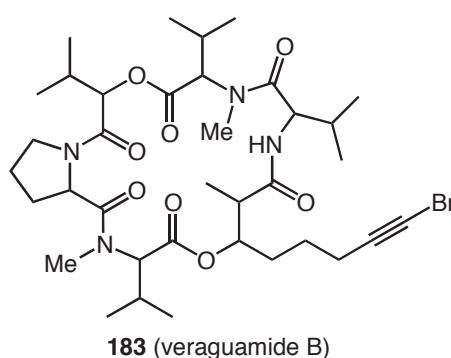


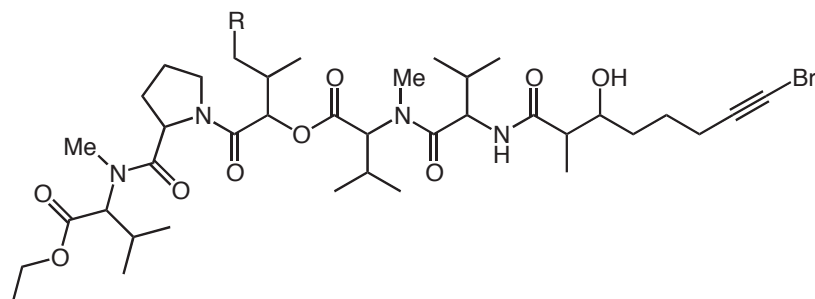
179 (bouillomide B)

A different cyanobacterium from Guam, *Lyngbya semiplena*, has afforded three new cyclodepsipeptides including the bromine-containing lyngbyastatin 10 (**180**).¹²² Another bromophenol, bisebromoamide (**181**), was identified in an Okinawan *Lyngbya* sp.,¹²³ but the original structure was revised slightly by total synthesis.¹²⁴

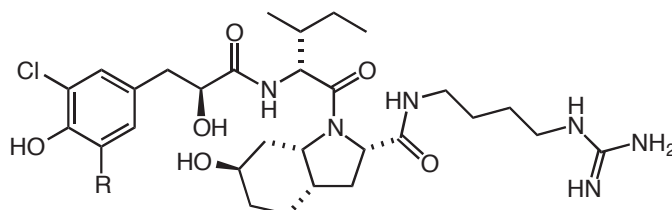
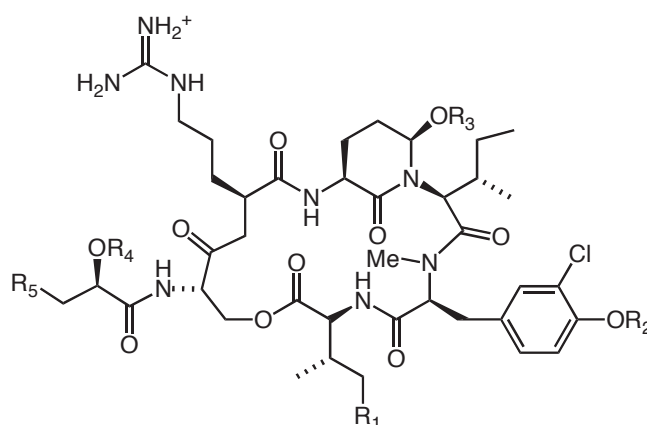
**180** (lyngbyastatin 10)**181** (bisebromoamide)

Two different cyanobacteria species, *Symploca* cf. *hydroides* from Guam¹²⁵ and *Oscillatoria margaritifera* from Panama,¹²⁶ contain the same collection of cyclic depsipeptides, the veraguamides, several of which contain the rare bromoacetylene function. Veraguamides A (**182**) and B (**183**) were found in both studies,^{125,126} while K (**184**) and L (**185**) were only characterized from *Oscillatoria margaritifera*.¹²⁶ Veraguamide A was quite potent against the H-460 human lung cancer cell line ($LD_{50} = 0.14 \mu\text{M}$).¹²⁶

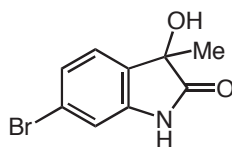
**182** (veraguamide A)**183** (veraguamide B)

**184** (veraguamide K) R = Me**185** (veraguamide L) R = H

The fresh water cyanobacterium *Microcystis* sp. from a water reservoir in Israel yielded the novel aeruginosins KY642 (**186**) and KY608 (**187**).¹²⁷ A different reservoir in Israel containing a *Microcystis aeruginosa* bloom afforded seven chlorinated protease inhibitor micropeptins: HU1069 (**188**), HU989 (**189**), HU1041 (**190**), HU975 (**191**), HU895A (**192**), HU909 (**193**), and HU895B (**194**).¹²⁸ These compounds inhibit trypsin with IC₅₀'s in the range 0.7-5.2 μM, and chymotrypsin with IC₅₀'s of 2.8-72 μM. The cyanobacterium *Anabaena constricta* has furnished the novel indole alkaloid bromoanindolone as an unequal mixture of both enantiomers (**195**).¹²⁹

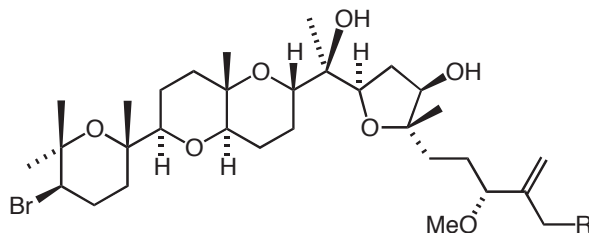
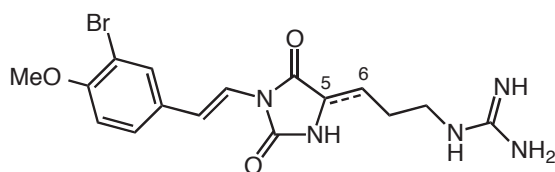
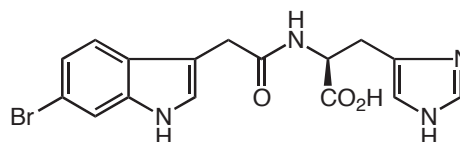
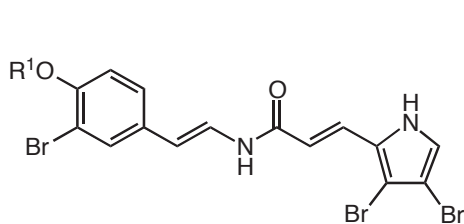
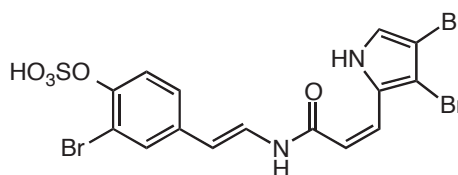
**186** (aeruginosin KY642) R = Cl**187** (aeruginosin KY608) R = H

	R ₁	R ₂	R ₃	R ₄	R ₅
188 (micropeptin HU1069)	Me	Me	H	SO ₃ ⁻	SO ₃ ⁻
189 (micropeptin HU989)	Me	Me	H	H	SO ₃ ⁻
190 (micropeptin HU1041)	H	H	H	SO ₃ ⁻	SO ₃ ⁻
191 (micropeptin HU975)	H	Me	H	H	SO ₃ ⁻
192 (micropeptin HU895A)	H	Me	H	H	H
193 (micropeptin HU909)	H	Me	Me	H	H
194 (micropeptin HU895B)	Me	H	H	H	H

**195** (bromoanaindolone)

J. Miscellaneous Marine Animals

Over the years the sea hare *Aplysia dactylomela* has provided synthetic chemists with a multitude of enticing target molecules. A recent examination of this animal from Puerto Rico has revealed the novel bromotriterpene polyethers aplysqualenol A (**196**) and B (**197**),¹³⁰ which are related to the well known thysiferol and suggestive of a dietary source for the sea hare. The sea anemone *Parazoanthus axinellae* contains five new hydantoin alkaloids, two of which are the bromine-containing parazoanthine D (**198**) and E (**199**).¹³¹ Bunodosine 391 (**200**) is a toxic component of the venom of the sea anemone *Bunodosoma cangicum*.¹³² This compound displays potent analgesic activity as mediated by serotonin receptors. The marine ciliate *Pseudokeronopsis riccii* contains the novel bromopyrrole keronopsamides A-C (**201-203**).¹³³

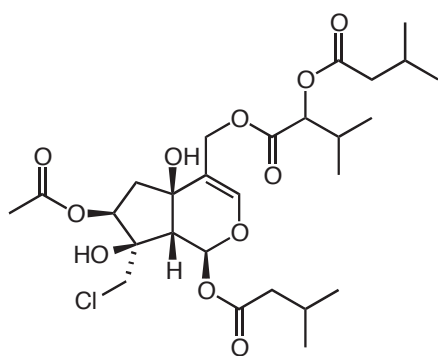
**196** (aplysqualenol A)**197** (aplysqualenol B)**198** (parazoanthine D)**199** (parazoanthine E) $\Delta^{5,6}$ **200** (bunodosine 391)**201** (keronopsamide A) $R^1 = H$ **202** (keronopsamide B) $R^1 = SO_3H$ **203** (keronopsamide C)

III. TERRESTRIAL ORGANISMS

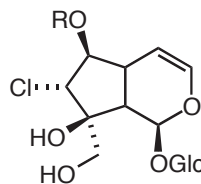
While fewer in overall numbers, terrestrial naturally occurring organohalogens have a longer history of discovery than marine organohalogens, and new examples continue to be unearthed. As in Section II, only new heterocyclic compounds discovered in 2009-2011 are presented.

A. Plants

Naturally occurring iridoids and secoiridoids, both chlorinated and non-chlorinated, have a long history in folk medicine as beneficial phytochemicals.¹³⁴ The roots of *Valeriana officinalis* from China have yielded volvaltrate B (**204**) along with a non-chlorine containing analogue.¹³⁵ Three new chlorinated iridoid glucosides, asystasioside E (**205**) and longifoliosides A (**206**) and B (**207**) were isolated from *Veronica longifolia*.¹³⁶ The latter two compounds display radical-scavenging activity. The Chilean plant *Mimulus glabratus* contains the new 6-chlorohalleridone (**208**), a rare 2-chlorocyclohexenone, along with halleridone, also known as renygolone.¹³⁷



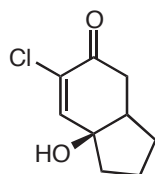
204 (valerianaceae)



205 (asystasioside E) R = H

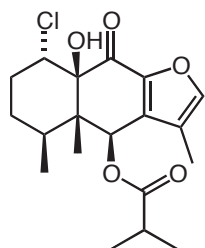
206 (longifolioside A) R = 3,4-di-OH-benzoyl

207 (longifolioside B) R = caffeoyl

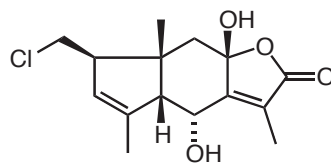


208 (6-chlorohalleridone)

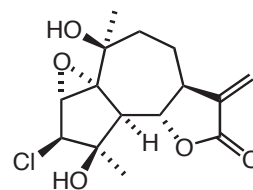
An investigation of the Chinese medicinal plant *Ligularia atroviolacea* has identified 24 compounds, including the new furoeremophilane derivative **209**.¹³⁸ Another Chinese herbal medicinal plant, *Lindera aggregata*, has afforded five new sesquiterpene lactones, including linderagalactone A (**210**), which possesses a novel rearranged carbon framework.¹³⁹ The Chinese perennial herb *Artemisia anomala*, which is also used in Chinese folk medicine as an analgesic and antibiotic, contains the new guaianolide artanomalide B (**211**).¹⁴⁰



209

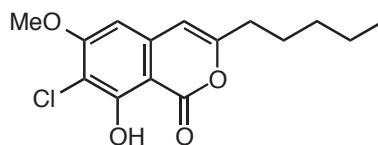


210 (linderagalactone A)

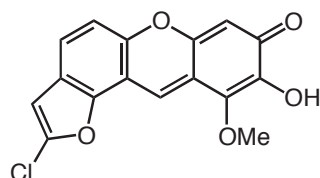


211 (artanomalide B)

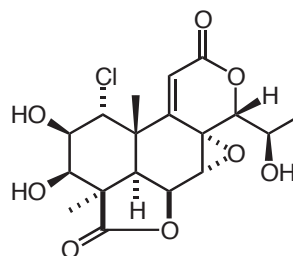
The Tanzanian tree *Tessmannia densiflora* produces the isocoumarin **212**,¹⁴¹ and the Chinese medicinal plant *Blumea riparia*, which is used to treat gynecological diseases, contains the novel xanthene blumeaxanthene II (**213**), the first example of a halogenated xanthene from a plant.¹⁴² The Asian evergreen tree *Podocarpus macrophyllus* contains the new makilactone E (**214**) along with several non-chlorinated bisnor- and norditerpene dilactones.¹⁴³ Crassifoside H (**215**) is a glucosyl-fused tetracyclic chlorophenol found in the Chinese folk medicine plant *Curculigo glabrescens*.¹⁴⁴



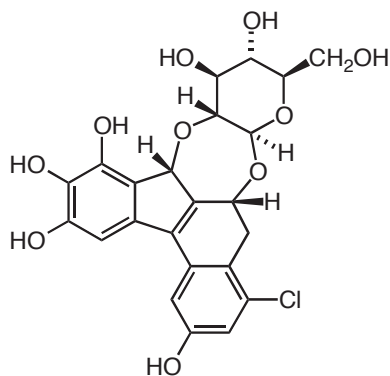
212



213 (blumeaxanthene II)

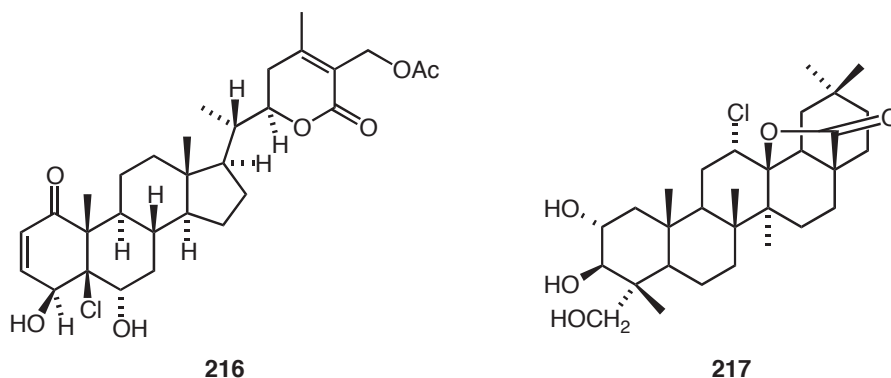


214 (makilactone E)



215 (crassifoside H)

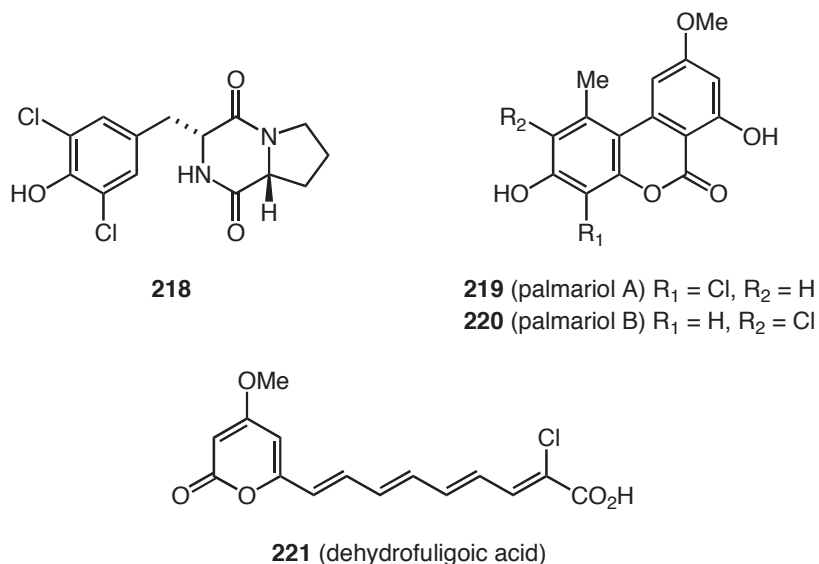
Although halogenated steroids are rare in nature, several chlorine-containing withanolides are known, and a recent example is **216**, isolated from the Pakistanian *Withania somnifera*.¹⁴⁵ The chloro lactone triterpenoid **217**, a derivative of the ubiquitous oleanolic acid, was characterized from the roots of *Actinidia chinensis*, a Chinese folk medicine anticancer plant.¹⁴⁶



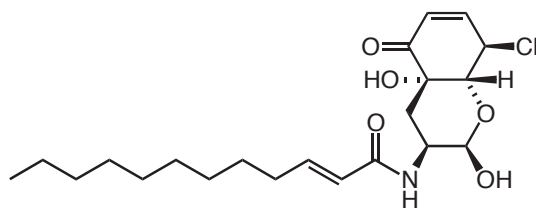
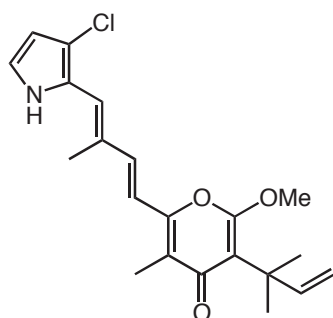
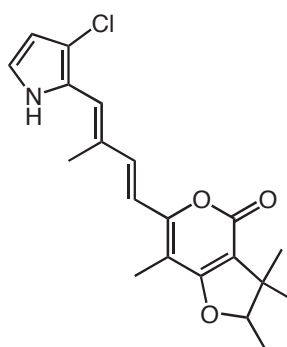
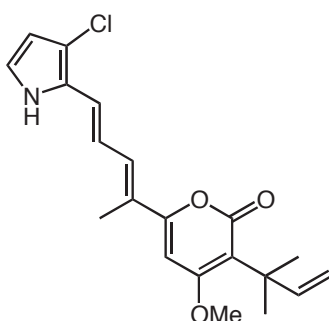
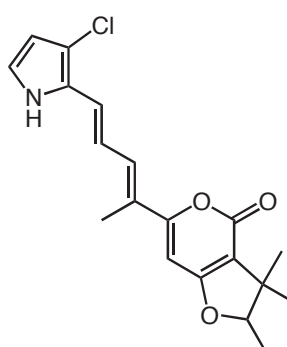
B. Fungi

Some of the earliest reported natural organohalogen compounds were described from terrestrial fungi; for example, drosophilin A methyl ether, sporidesmin A, 2,4-dichlorophenol, ascochlorin, and chloromethane.⁴

The fungus *Leptoxyphium* sp., also known as genus *Caldariomyces*, contains the new dichlorodiketopiperazine **218**, which is 10-20 times more active than the nonchlorinated analogue in the inhibition of CCL2-induced chemotaxis.¹⁴⁷ The Japanese discomycete fungus *Lachnum palme* has afforded the novel dibenzo- α -pyrones palmariol A (**219**) and B (**220**).¹⁴⁸ Dehydrofulgic acid (**221**) is a novel yellow polyene-pyrone that is found in the mushroom *Fuligo septica* f. *flava*.¹⁴⁹

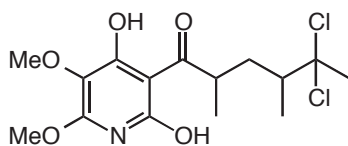


The parasitic fungus *Isaria tenuipes* produces the novel bicyclic hemiacetal isariotin F (**222**). In addition to its infection of insect pupae and larvae, isariotin F exhibits activity against the malaria parasite and displays activity in several human cancer cell lines.¹⁵⁰ Four of the six photosensitive polyketide malbranpyrroles isolated from the thermophilic *Malbranchea sulfurea* fungus living in fumarole soil in Taiwan are the 3-chloropyrrole derivatives malbranpyrroles C-F (**223-226**).¹⁵¹ Unlike these latter metabolites, the two nonchlorinated compounds were not cytotoxic against several human cancer cell lines.

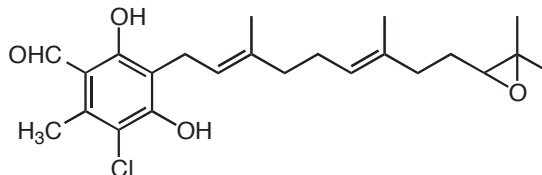
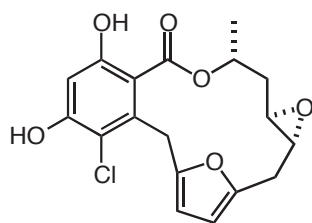
**222** (isariotin F)**223** (malbranpyrrole C)**224** (malbranpyrrole D)**225** (malbranpyrrole E)**226** (malbranpyrrole F)

A new atpenin, NBRI23477 A (**227**), was isolated from the fermentation broth of *Penicillium atramentosum* PF1420 from a Japanese soil sample. This novel chlorine-containing pyridine inhibited the growth of the human prostate cancer DU-145 cell line.¹⁵² The ascochlorin precursor LL-Z1272 α epoxide (**228**) is produced by a mutant of *Ascochyta viciae*.¹⁵³ Two studies of the fungus *Pochonia*

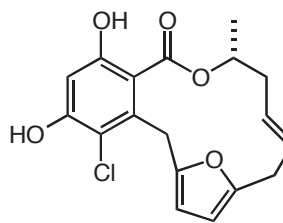
chlamydosporia var. *chlamydosporia* have harvested nine new chlorinated radicicol analogues, pochonins G-I (229-231)¹⁵⁴ and K-P (232-237).¹⁵⁵ Like the well known radicicol, these pochonins inhibit WNT-5A expression. WNT-5A is a secretory glycoprotein implicated in hair loss.



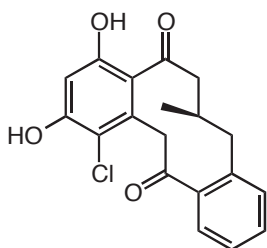
227 (NBRI23477 A)

228 (LL-Z1272 α epoxide)

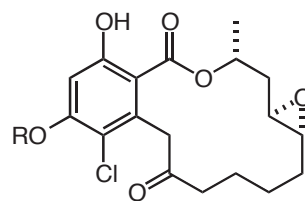
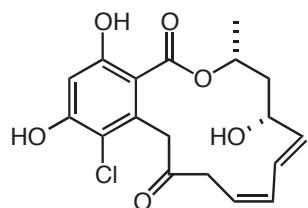
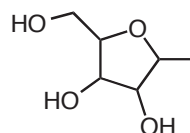
229 (pochonin G)



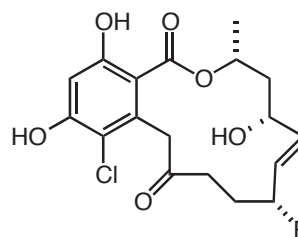
230 (pochonin H)



231 (pochonin I)

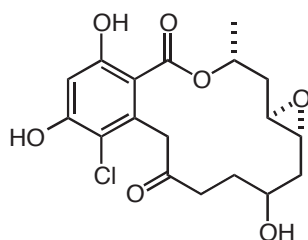
232 (pochonin K) R = 

233 (pochonin L)

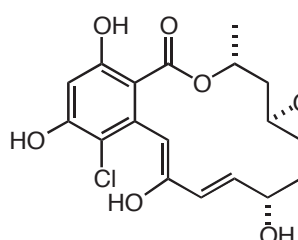


234 (pochonin M) R = H

235 (pochonin N) R = OH

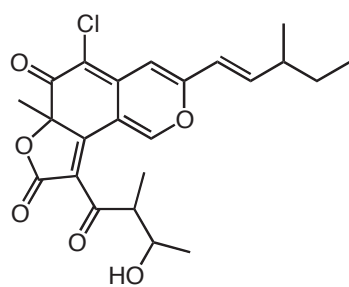
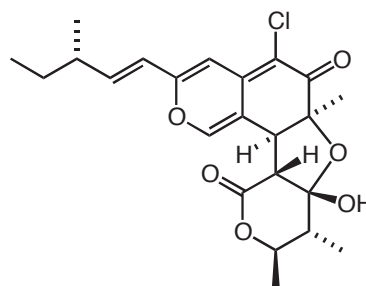
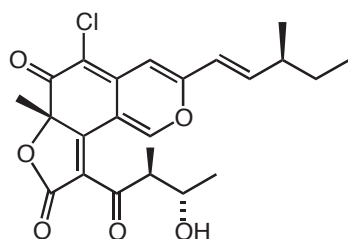
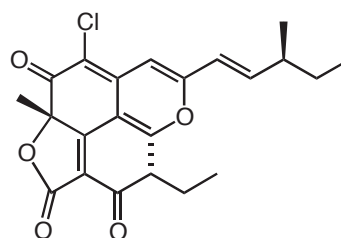
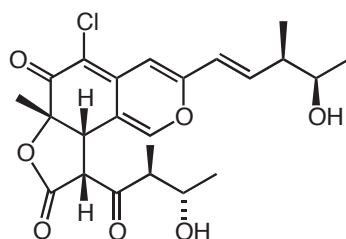
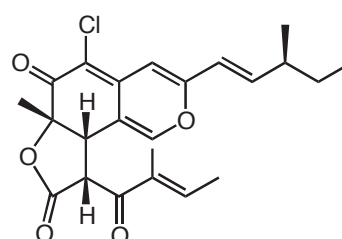


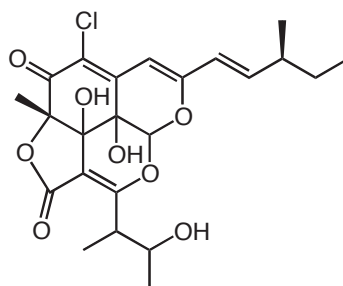
236 (pochonin O)



237 (pochonin P)

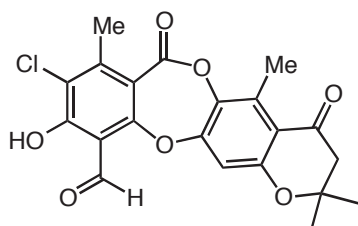
The azaphilones are a large collection of related fungal metabolites produced via a polyketide biosynthesis and numbering nearly 200 compounds, many of which contain chlorine.¹⁵⁶ The name for these biologically active compounds derives from their facile reaction with nitrogen nucleophiles ("aza-Michael" acceptors). Several new azaphilones have been reported in the past three years. A study of the microfungus *Chaetomium* sp., obtained from emu scat, resulted in the isolation of the new chaetoviridin E (**238**) and revision of the previously known chaetoviridins B and D.¹⁵⁷ Chaetoviridin E is a diastereomer of chaetoviridin A. Chaetomugilin D (**239**) was isolated from *Chaetomium globosum*, an endophytic fungus growing on the Chinese medicinal plant *Ginkgo biloba*.¹⁵⁸ This new azaphilone is the dehydroxy analogue of the previously known chaetomugilin A, which was also found in this fungus. A separate study of this fungus found growing on the leaves of *Viguiera robusta* yielded five new chlorinated azaphilones, 5'-epichaetoviridin A (**240**), 4'-epichaetoviridin F (**241**), 12 β -hydroxychaetoviridin C (**242**), and chaetoviridins G (**243**) and H (**244**).¹⁵⁹ The absolute configuration of **240** was determined by Mosher's method.

**238** (chaetoviridin E)**239** (chaetomugilin D)**240** (5'-epichaetoviridin A)**241** (4'-epichaetoviridin F)**242** (12 β -hydroxychaetoviridin C)**243** (chaetoviridin G)

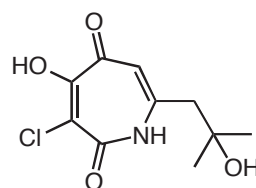


244 (chaetoviridin I)

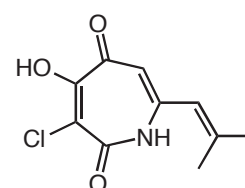
The fungus *Chaetomium brasiliense* from Thailand afforded ten mollicellins, four of which are new and one of these, mollicellin M (**245**), is chlorinated.¹⁶⁰ All of these mollicellins show antimalarial, antifungal, anti-tuberculosis, and anticancer activity to some degree. The endophytic microfungus *Pestalotiopsis* sp., grown on damp white rice, yielded the novel caprolactams, pestalactams A-C, two of which, A (**246**) and C (**247**), are chlorinated.¹⁶¹



245 (mollicellin M)

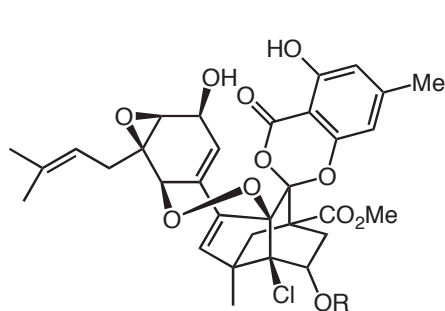


246 (pestalactam A)

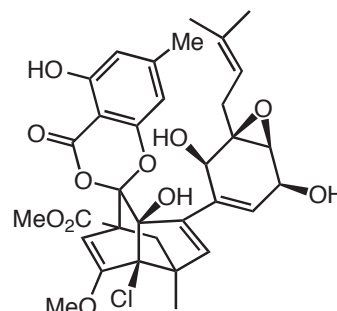


247 (pestalactam C)

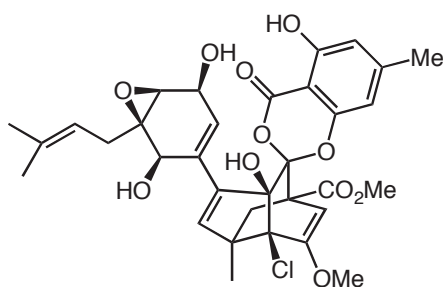
The endophytic fungus *Pestalotiopsis fici* was isolated from the branches of the tea plant (*Camellia sinensis*) in China and cultured to yield the five chlorinated chloropupukeanolides A-E (**248-252**) and chloropupukeanone A (**253**).^{162,163} These stunningly complex natural products, which show significant anti-HIV and cytotoxic activity, feature a chloropupukeanane core, a novel spiroketal peroxide (**248** and **249**),¹⁶² and a chlorinated tricyclo[4.3.1.0^{3,7}]decane ring system suggestive of a Diels-Alder biosynthesis.^{162,163} Chloropestolide A (**254**) is another member of this extraordinary structural class.¹⁶⁴



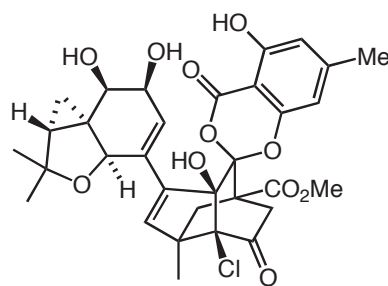
248 (chloropupukeanolide A) R = Me
249 (chloropupukeanolide B) R = H



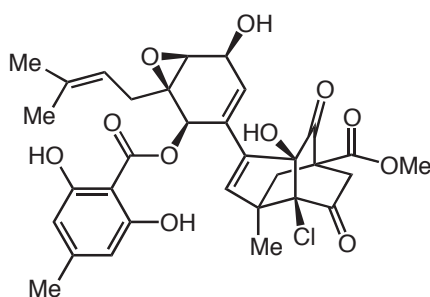
250 (chloropupukeanolide C)



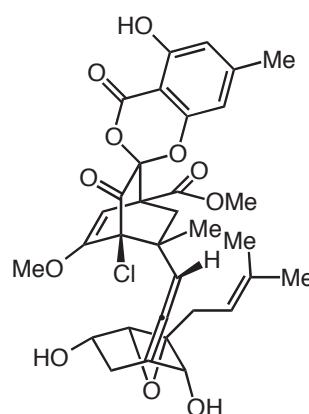
251 (chloropupukeanolide D)



252 (chloropupukeanolide E)



253 (chloropupukeanone A)

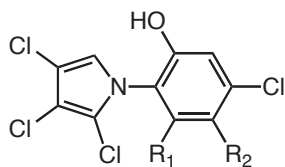
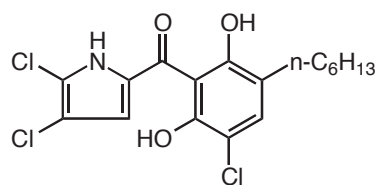
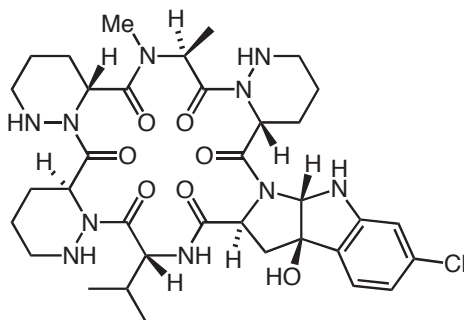


254 (chloropestolide A)

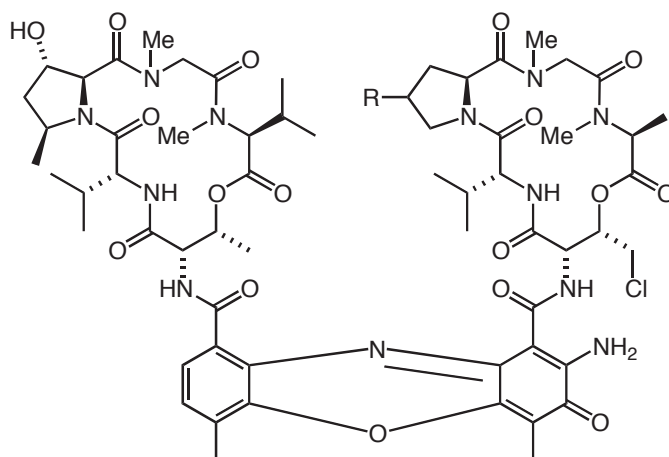
C. Bacteria

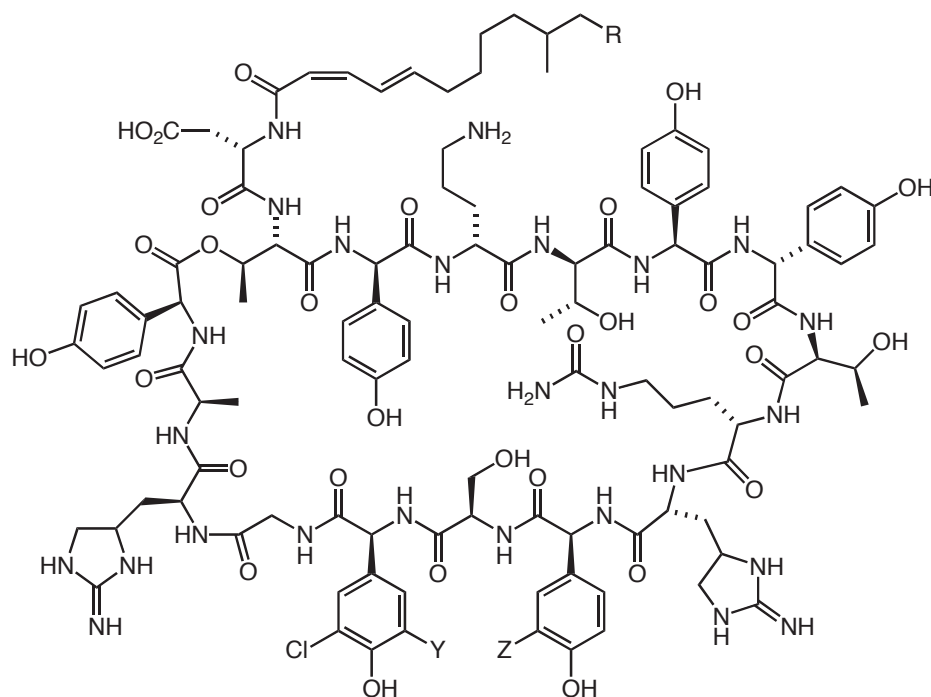
Terrestrial bacteria have a long and rich history in providing structurally unique and biologically potent halogenated natural products, the epitome being vancomycin, which has been used for 60 years to treat penicillin-resistant infections.

The three novel antibiotics, neopyrrolomycins B-D (**255-257**), are potent against Gram-positive pathogens and were obtained from a *Streptomyces* sp., which was isolated from an Arizona watershed soil sample.¹⁶⁵ The closely related neopyrrolomycin A was characterized in 1990. The structure of celeastramycin A (**258**) has been revised by total synthesis.¹⁶⁶ This *Streptomyces* sp. metabolite suppresses the production of IL-8 (IC₅₀ 0.06 μg/mL) in human endothelial cells. A soil sample from the Shaanxi province of China contains *Streptomyces alboflavus*, which produces NW-G01 (**259**), a novel cyclic hexadepsipeptide antibiotic, with strong antibacterial activity against *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, and methicillin-resistant *Staphylococcus aureus*.¹⁶⁷⁻¹⁶⁹

**255** (neopyrrolomycin B) $R_1 = \text{Cl}$, $R_2 = \text{Cl}$ **256** (neopyrrolomycin C) $R_1 = \text{Cl}$, $R_2 = \text{H}$ **257** (neopyrrolomycin D) $R_1 = \text{H}$, $R_2 = \text{Cl}$ **258** (celsastramycin A)**259** (NW-G01)

Another *Streptomyces* sp. from an Australian soil sample has afforded two novel chlorinated actinomycins, Y_1 (**260**) and Y_2 (**261**).¹⁷⁰ Genetically engineered *Streptomyces fungicidicus* has yielded three new enduracidin analogues **262-264**.¹⁷¹

**260** (actinomycin Y_1) $R = \text{O}$ **261** (actinomycin Y_2) $R = \text{OH}$



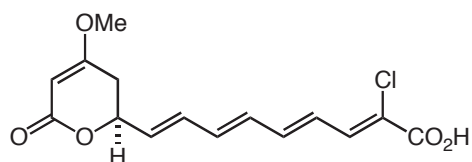
262 (monodeschloroenduracidin A) R = H, Y = Z = H

263 (monodeschloroenduracidin B) R = Me, Y = Z = H

264 (enduracidin) R = H, Y = Z = Cl

D. Slime Molds

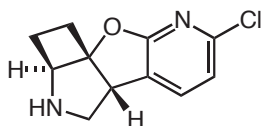
Fuligoic acid (**265**) is a novel chlorinated polyene-pyrone found in the slime mold (myxomycete) *Fuligo septica* f. *flava*.¹⁷²



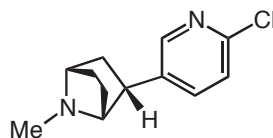
265 (fuligoic acid)

E. Higher Animals

The Ecuadorian poison frog *Epipedobates anthonyi*, which contains the famous epibatidine, also possesses the novel alkaloid phantasmidine (**266**) along with *N*-methylepibatidine (**267**).¹⁷³ Both of these alkaloids display activity at nicotinic acetylcholine receptors, although phantasmidine has an altered selectivity relative to epibatidine.



266 (phantasmidine)



267 (*N*-methylepibatidine)

IV. SUMMARY

The field of organohalogen natural products has truly blossomed into an enormous scientific discipline. Ironically, evidence indicates that organohalogen compounds — both biotic and abiotic — have been on earth for centuries if not eons. Microfossils in Precambrian rocks, which are a billion years old, are identical to the cyanobacterium *Nostoc*, and other microfossils are morphologically indistinguishable from *Oscillatoria*, two present-day species rich in organohalogen metabolites.¹⁷⁴

Several studies have identified polychlorinated dibenzo-*p*-dioxins and dibenzofurans in ancient sediments, which may have both a biotic and abiotic origin. Some halogenated bipyrrroles (e.g., **157**) and polybrominated diphenyl ethers were discovered in an archived sample of whale oil from the 1921 final voyage of the *Charles W. Morgan* whaling ship.¹⁷⁵

Studies of emissions from several volcanoes have uncovered a large number of organohalogens, including heterocycles.¹⁷⁶ Given the discovery of hydrogen chloride and hydrogen fluoride in interstellar space,^{177,178} it is tantalizing to foresee the identification of organohalogen compounds amongst the more than 100 stable organic compounds already detected in interstellar space.¹⁷⁹ Peatlands, which comprise 2% of the earth's continental surface, have accumulated 280-1,000 million tons of organochlorines during the postglacial period.¹⁸⁰

But what is the *raison d'être* for natural organohalogens? This is the big question! Some organohalogens function as recyclers of halogen, as pheromones and hormones, as natural pesticides and anti-feedants, as anti-foulants, and as structural proteins. The benefit to mankind is that many organohalogen compounds display enormous biological activity that may lead to clinical drugs. Indeed, most of these promising compounds are heterocycles.

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