CHAPTER 1

Occurrence of Halogenated Alkaloids

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Contents

I. INTRODUCTION

This review is an outgrowth of two previous comprehensive surveys by the present author of all known naturally occurring organohalogen compounds.[1,2] Coverage in the present review is limited to halogenated alkaloids. With the exception of halogenated tyrosines, which were expertly covered by Peng et al. in this series in 2005,[3] the present review attempts full coverage of halogenated alkaloids. It should be noted that halogenated amino acids and their derivatives and miscellaneous nitrogen-containing metabolites that are generally considered not to be alkaloids (e.g., macrolides, tetracyclines, enediynes, malyngamides) are not treated in this review.

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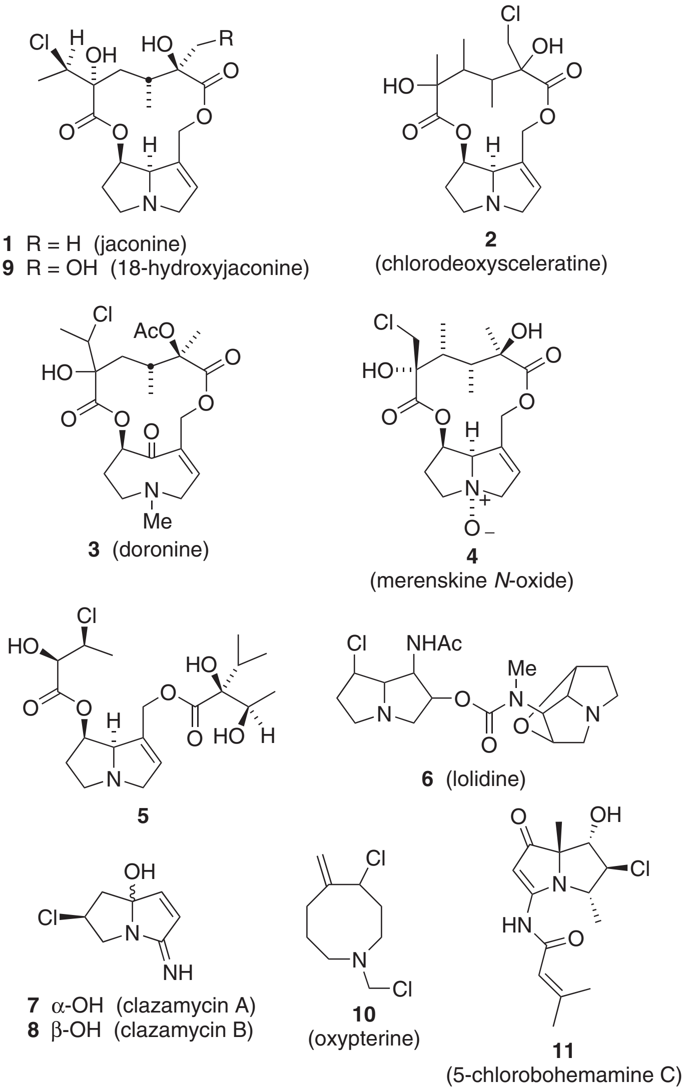
II. OCCURRENCE

A. Pyrrolizidine, Indolizidine, and Related Alkaloids

A small group of chlorine-containing pyrrolizidine alkaloids seem to be the first examples of halogenated alkaloids of any type to be identified (Figure 1). Thus, jaconine (**1**) was isolated from *Senecio jacobaea* in 1937.[4–9]



1 R = H (jaconine)
9 R = OH (18-hydroxyjaconine)

2
(chlorodeoxysceleratine)

3 (doronine)

4
(merenskine *N*-oxide)

5

6 (lolidine)

7 α-OH (clazamycin A)
8 β-OH (clazamycin B)

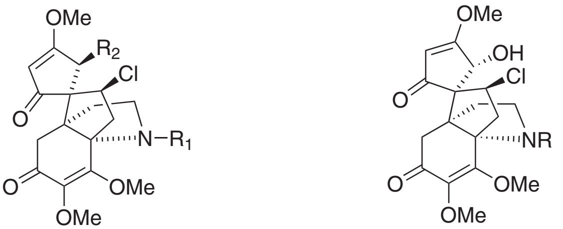
10
(oxypterine)

11
(5-chlorobohemamine C)

Figure 1 Chlorinated pyrrolizidine and related alkaloids **1–11**.

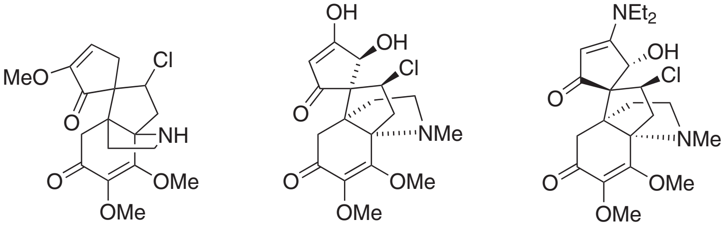
This plant, "tansy ragwort," is highly toxic to cattle and other livestock, as are other *Senecio* sp. plants.[10,11] Other members of these pyrrolizidine and related chlorohydrins are chlorodeoxysceleratine (**2**) (*Senecio sceleratus*),[12] doronine (**3**) (*Doronicum macrophyllum*),[13] merenskine *N*-oxide (**4**) (*Senecio latifolius*),[14] alkaloid **5** (*Cryptantha clevelandii* and *C. leiocarpa*),[15] lolidine (**6**) (*Lolium cuneatum*),[16] and clazamycins A (**7**) and B (**8**) (*Streptomyces* sp.).[17,18] A new addition to this group is 18-hydroxyjaconine (**9**) (*Senecio selloi*).[19] Jaconine was also isolated from *Senecio alpinus*,[20] and doronine was found in *S. clevelandii*[21] and *S. abrotanifolius*.[22] The most implausible structure **10** was put forth for oxypterine (*Lotononis oxytera*),[23] which, if correct, is a "ring-opened" pyrrolizidine. "Antibiotic 354" from cultures of *Streptomyces pumiceus* subsp. *doliceus* seems to be identical with clazamycin B (**8**).[24] A marine cultured *Streptomyces* sp. has furnished the chlorohydrin 5-chlorobohemamine C (**11**), which was demonstrated not to be an isolation artifact.[25]

Several organochlorine plant alkaloids of the hasubanan type are known, characterized by the prototypes acutumine (**12**), acutumidine (**13**), and acutuminine (**14**), which were initially isolated from *Sinomenium acutum* and *Menispermum dauricum*[26–30] and later from *M. canadense*[31] (Figure 2). The corresponding epimers, dauricumine (**15**) and dauricumidine (**16**), were found in *M. dauricum*.[32] Clolimalongine (**17**) is present in *Limacia oblonga*,[33] and 2-*O*-demethylacutumine (**18**) was isolated from *Sinomenium acutum*.[34] The



12 R_1 = Me, R_2 = OH (acutumine)
13 R_1 = H, R_2 = OH (acutumidine)
14 R_1 = Me, R_2 = H (acutuminine)

15 R = Me (dauricumine)
16 R = H (dauricumidine)



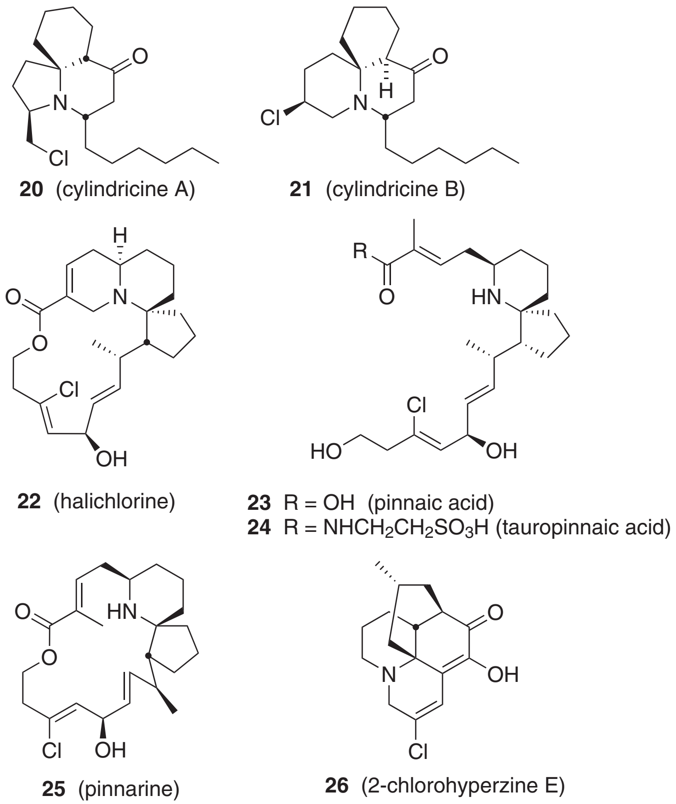
17 (clolimalongine) **18** (2-*O*-demethylacutumine) **19** (hypserpanine A)

Figure 2 Chlorinated hasubanan type alkaloids **12–19**.

diethylamino analog of dauricumine, hypserpanine A (**19**) was characterized in the Chinese medicinal herb *Hypserpa nitida* Miers. (Menispermaceae).[35]

The saturated 1*H*-pyrrolo[2,1-*j*]quinoline ring system is present in cylindricine A (**20**), in equilibrium with cylindricine B (**21**), both of which are found in the Tasmanian ascidian *Clavelina cylindrical*[36] (Figure 3). These novel alkaloids are in equilibrium via an aziridinium ion in a well-known process.[37] These biologically active halichlorine (**22**), from the black marine sponge *Halichondria okadai*,[38,39] and pinnaic acid (**23**) and tauropinnaic acid (**23**), from the bivalve *Pinna muricata*,[40] have received intense synthetic interest and led to both confirmation and revision of the original structures.[41,42] A new member of the halichlorine family is pinnarine (**25**) from *Halichondria okadi*.[43] The Chinese medicinal plant *Hyperzia serrata* contains 2-chlorohyperzine E (**26**).[44]

A culture of *Aspergillus fischeri* var. *thermomutatus* produces CJ-12662 (**27**) and UK-88051 (**28**)[45] (Figure 4). The Ecuadorian poison frog *Epipedobates anthonyi* (=*Epipedobates tricolor*=*Dendrobates tricolor*) contains



20 (cylindricine A)

21 (cylindricine B)

22 (halichlorine)

23 R = OH (pinnaic acid)
24 R = $NHCH_2CH_2SO_3H$ (tauropinnaic acid)

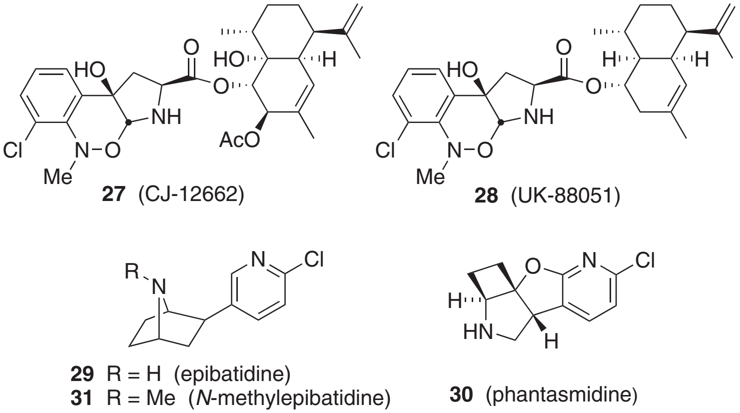
25 (pinnarine)

26 (2-chlorohyperzine E)

Figure 3 Chlorinated pyridoquinoline and related alkaloids **20–26**.

the remarkably active epibatidine (**29**)[46,47] along with phantasmidine (**30**) and *N*-methylepibatidine (**31**).[48] The story of epibatidine has been reviewed.[49–52]

The first chromone to be discovered in a marine invertebrate is tubastraine (**32**), which is found in the stony coral *Tubastraea microantha*[53] (Figure 5). This organism is able to thwart attack by the destructive Crown-of-Thorns sea star, perhaps because of tubastraine. The soil fungus



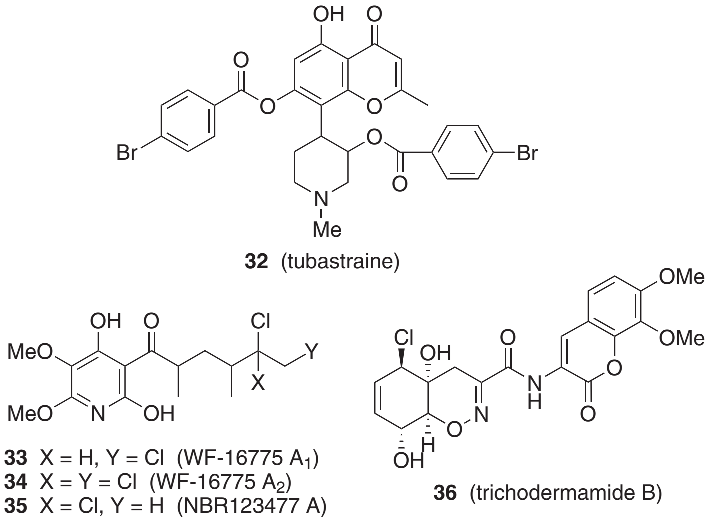
27 (CJ-12662)

28 (UK-88051)

29 R = H (epibatidine)
31 R = Me (*N*-methylepibatidine)

30 (phantasmidine)

Figure 4 Chlorinated alkaloids **27**–**31**.



32 (tubastraine)

33 X = H, Y = Cl (WF-16775 A_1)
34 X = Y = Cl (WF-16775 A_2)
35 X = Cl, Y = H (NBR123477 A)

36 (trichodermamide B)

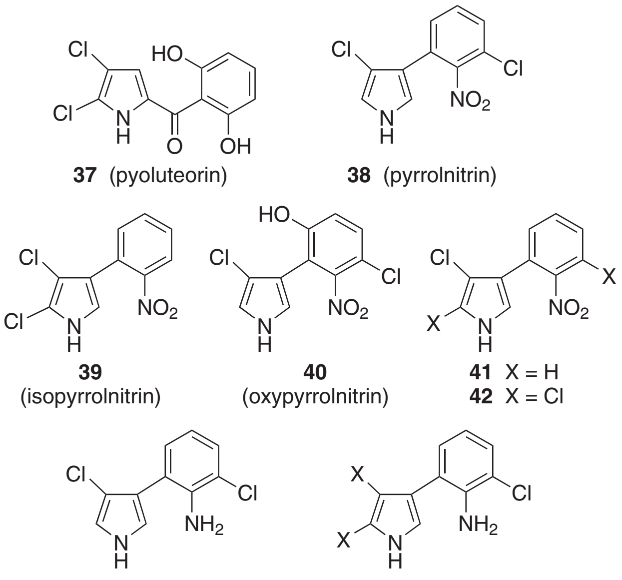
Figure 5 Halogenated alkaloids **32**–**36**.

Chaetasbolisia erysiophoides has yielded the novel angiogenesis inhibitors WF01-16775 A_1 (**33**) and A_2 (**34**).[54] The related NBR123477 A (**35**) was characterized from a fermentation broth of *Penicillium atramentosum* PF1420 from a Japanese soil sample.[55] This highly substituted pyridine inhibits the growth of the human prostate cancer DU-145 cell line. The marine fungus *Trichoderma virens* provides the unusual trichodermamide B (**36**), which is quite active against HCT-116 human colon carcinoma.[56] The nonchlorinated trichodermamide A is devoid of biological activity in all assays tested.

B. Pyrroles

One of the largest classes of halogenated alkaloids is pyrroles, both brominated and chlorinated, of many types. This is not surprising given the enormous reactivity of the pyrrole ring in electrophilic substitution, some 3×10^{18} times faster than benzene in electrophilic bromination[57]!

Pseudomonas bacteria are a rich source of halogenated pyrroles, exemplified by pyoluteorin (**37**) and pyrrolnitrin (**38**), the former occurs in *P. aeruginosa*[58,59] and *P. fluorescens*,[60] and the latter occurs in *P. pyrrocinia*,[61,62] *P. aureofaciens*,[63,64] and *P. cepacia*[65] (Figure 6). Pyrrolnitrin is also produced



37 (pyoluteorin)

38 (pyrrolnitrin)

39 (isopyrrolnitrin)

40 (oxypyrrolnitrin)

41 X = H
42 X = Cl

43 (aminopyrrolnitrin)

44 X = Cl
45 X = H

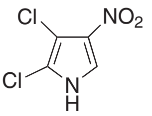
Figure 6 Chloropyrrole alkaloids **37–45**.

by *Enterobacter agglomerans*.[66] Other related halopyrroles are isopyrrolnitrin (**39**) (*P. pyrrocinia*),[67] oxypyrrolnitrin (**40**) (*P. pyrrocinia*),[68] **41** (*P. pyrrolnitrica*),[69] **42** (*P. fluorescens*)[70] (*P. cepacia*)[65] (*P. aureofaciens*),[71] aminopyrrolnitrin (**43**) (*P. cepacia*),[65] (*P. aureofaciens*),[71] **44** (*P. cepacia*),[65] and **45** (*P. aureofaciens*).[64]

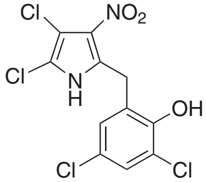
The potent microbial antibacterial pyrrolomycin A (**46**) and B (**47**) are produced by an *Actinomyces* sp., [72,73] and **47** is also found in cultures of *Streptomyces*.[74] Pyrrolomycins C (**48**), D (**49**), and E (**50**) are found in cultures of *Actinosporangium vitaminophilum*[75,76] (Figure 7).

Streptomyces sp. produce the optically active pyrroxamycin (**51**)[77] and the optically active neopyrrolomycin A (**52**)[78] (Figure 8). The former metabolite was also described as LL-F42248α in another study.[835] The three additional neopyrrolomycins B (**53**), C (**54**), and D (**55**) were isolated from an Arizona watershed soil *Streptomyces* sp.[79] Pyrrole **53** was isolated in an optically active form, but **54** and **55** exhibited no optical activity. The structure of celastramycin A (**56**) isolated from a *Streptomyces* strain[80] has been revised by total synthesis.[81] The acyl group was incorrectly thought to be attached to C3 of the pyrrole.

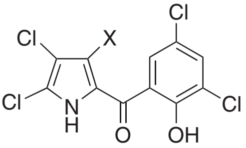
A culture of *Streptomyces fumanus* has yielded pyrrolomycins G (**57**), H (**58**), I (**59**), and J (**60**), and the absolute configuration of **57** and **58** was established as *S* [82] (Figure 9). Pentabromopseudilin (**61**) is produced by the marine bacteria *Pseudomonas bromoutilis*[83–85] and *Chromobacterium* sp.[86] Pentachloropseudilin (**62**) was found in cultures of *Actinoplanes* from an Indian soil sample.[87] The unprecedented benzofuro[3,2-*b*]pyrrole **63** was isolated from a *Pseudoalteromonas* sp. on the surface of an unidentified Hawaiian nudibranch.[88] The novel "biodegraded" (oxidized) pyrrolnitrins **64** and **65** were isolated from *Burkholderia cepacia* K87.[89]



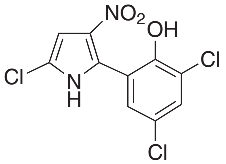
46 (pyrrolomycin A)



47 (pyrrolomycin B)

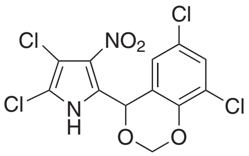


48 X = H (pyrrolomycin C)
49 X = Cl (pyrrolomycin D)

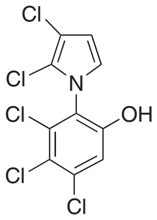


50 (pyrrolomycin E)

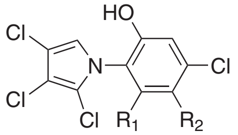
Figure 7 Chlorinated pyrrolomycin alkaloids **46–50**.



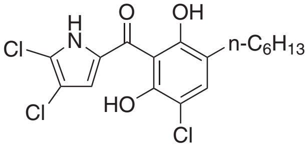
51 (pyrroxamycin)



52 (neopyrrolomycin A)

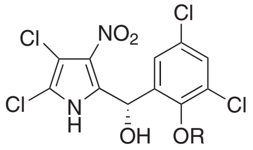


53 (neopyrrolomycin B) R_1 = Cl, R_2 = Cl
54 (neopyrrolomycin C) R_1 = Cl, R_2 = H
55 (neopyrrolomycin D) R_1 = H, R_2 = Cl

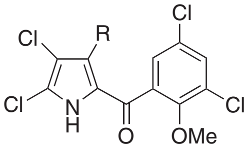


56 (celastramycin A)

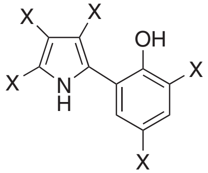
Figure 8 Pyrroxamycin and related chloropyrrole alkaloids **51**–**56**.



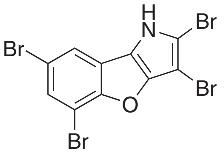
57 R = H (pyrrolomycin G)
58 R = Me (pyrrolomycin H)



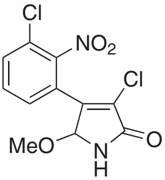
58 R = H (pyrrolomycin I)
60 R = Cl (pyrrolomycin J)



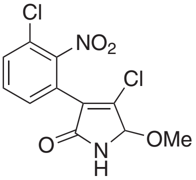
61 X = Br (pentabromopseudilin)
62 X = Cl (pentachloropseudilin)



63



64



65

Figure 9 Additional halogenated pyrrole alkaloids **57**–**65**.

An extraordinarily large number of simple halopyrroles are found in nature (Figures 10 and 11). The marine bacterium *Chromobacterium* sp. produces 2,3,4,5-tetrabromopyrrole (**66**) and 2,2′-bipyrrole **67**,[86] and the marine worm *Polyphysia crassa* secretes the antibacterial 2,3,4-tribromopyrrole (**68**), an extremely labile compound whose structure was confirmed by synthesis.[90] Although marine bacteria are rapidly becoming an important source of new natural products, sponges remain a prodigious producer of marine halogenated alkaloids. An early example is oroidin (**69**) from *Agelas oroides*, a sponge from the Bay of Naples.[91,92] This sponge also contains the simple pyrroles **70–72**,[91] as does *A. flabelliformis* from the Bahamas.[93] *Agelas* sp. sponges contain 2,3-dibromopyrrole (**73**) and **74–77**, [94] as do the sponges *Axinella damicornis* and *Stylissa flabelliformis*.[95]

These latter two sponges also produce the new **78–80**.[95] A Red Sea sponge *Acanthella carteri* contains **81**[96] and the Papua New Guinean *Agelas nakamurai* yields **82** and **83**.[97] Dibromo **84** was isolated from the Japanese sponge *Homaxinella* sp.,[98] and the simple ester **85** was characterized from the Sri Lanka sponge *Lissodendoryx* sp.[99] The debromo analog of **84** (**86**) was found in the Corsican sponge *Axinella verrucosa*.[100]

The sponge *Homaxinella* sp. also contains the enantiomeric lactams **87** and **88**,[98] and **87** was found in the Indian sponge *Agelas ceylonica*[101] (Figure 12). Longamide (**89**) was first described from *Agelas longissima*,[102] and the racemic esters **90–91**, known as hanishin, were isolated from the Red Sea sponge *Acanthella carteri*.[96] An optically active debromo analog of **87** (**92**) was obtained from the Indian sponge *Axinella tenuidigitata*,[103]

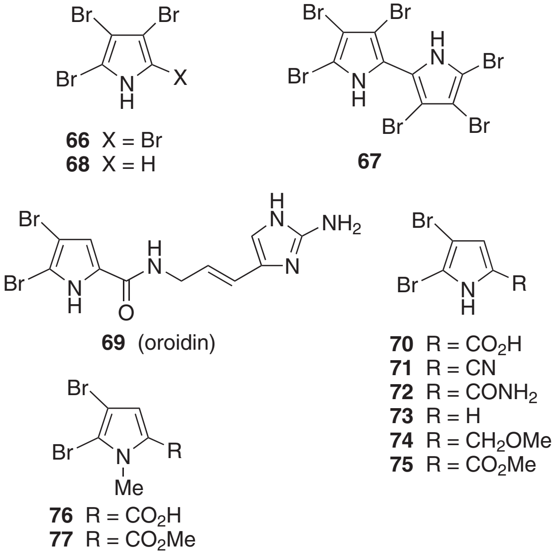


Figure 10 Bromopyrrole alkaloids **66–77**.

and the Caribbean *Agelas dispar* yielded longamide B (**93**).[104] The Micronesian *Axinella carteri* contains debromolongamide **94**,[105] which was also identified as "mukanadin C" in *Agelas nakamurai*.[106] Sponge metabolites **90**, **93**, and **87** have the *S* configuration as shown by total synthesis.[107]

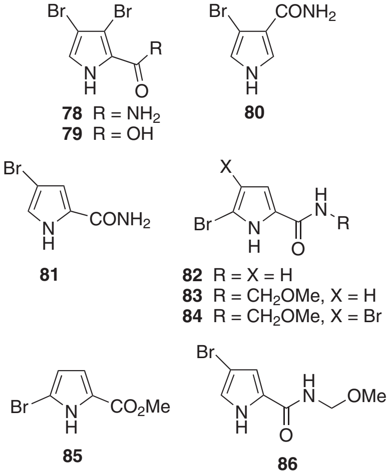

78 R = NH_2
79 R = OH
80
81
82 R = X = H
83 R = CH_2OMe, X = H
84 R = CH_2OMe, X = Br
85
86

Figure 11 Bromopyrrole alkaloids **78**–**86**.

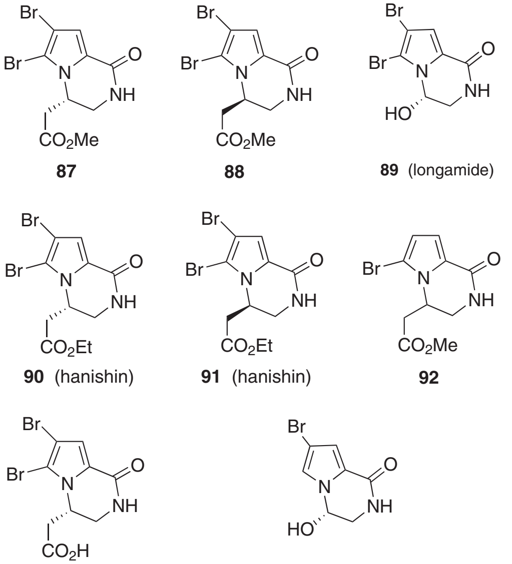
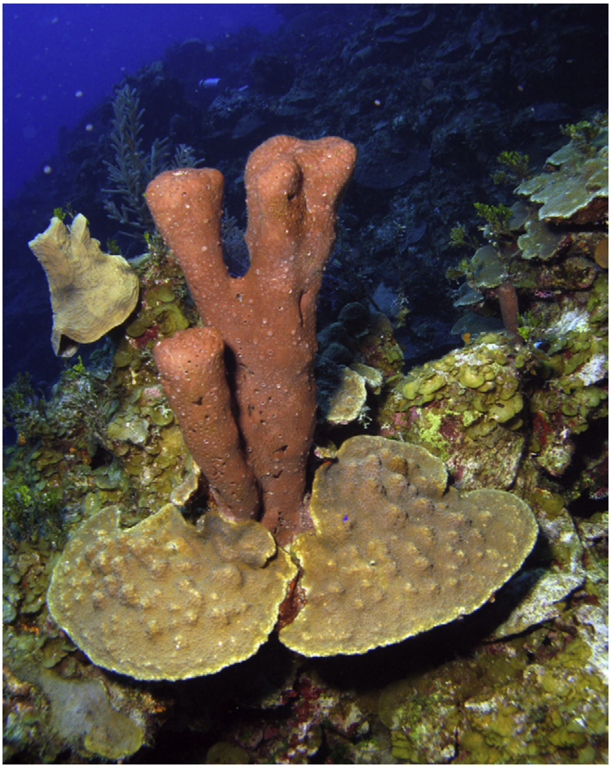

87
88
89 (longamide)
90 (hanishin)
91 (hanishin)
92
93 (longamide B)
94 (debromolongamide = mukanadin C)

Figure 12 Bromopyrrole lactam alkaloids **87**–**94**.



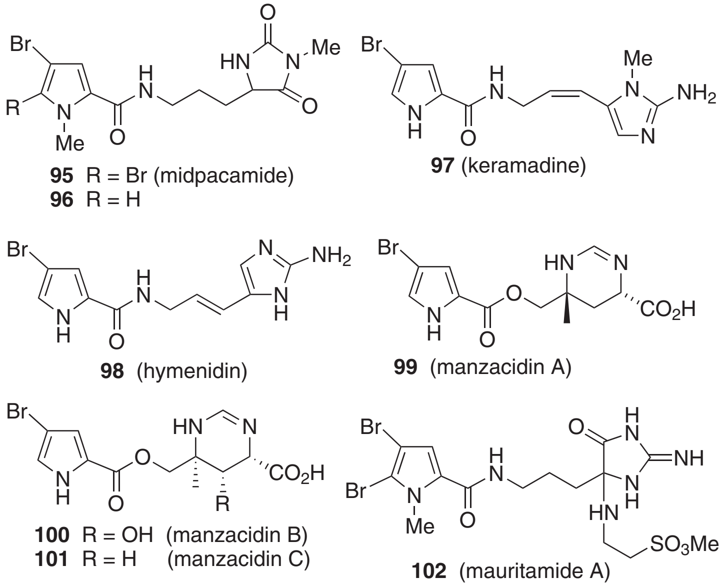
Agelas dispar A marine sponge that produces longamide B **93**.

Photo 1: Professor Joseph R. Pawlik.

Midpacamide (**95**) and 5-debromomidpacamide (**96**) were found in *Agelas mauritiana*,[108] and **95** was characterized earlier from a Marshall Islands sponge[109] (Figure 13). The related keramadine (**97**) was isolated from an Okinawan *Agelas* sponge and is a novel antagonist of serotonergic receptors,[110] and hymenidin (**98**) (monodebromooroidin) was found in an Okinawan *Hymeniacidon* sp. sponge.[111] This latter sponge also furnishes manzacidins A (**99**), B (**100**), and C (**101**), the first examples of marine tetrahydropyrimidines.[112,113, 114] In addition to containing midpacamide (**95**), a Fijian *Agelas* sp. sponge yielded mauritamide A (**102**).[115]

A collection of the newly cataloged Indonesian *Agelas linnaei* afforded several new bromopyrroles (**103–108**) including the novel taurine analogu **109**[116] (Figure 14).

The Mediterranean sponge *Axinella damicornis* contains damipipecolin (**110**) and damituricin (**111**)[117] (Figure 15). The Caribbean *Agelas dispar* (*vide supra*) and *Agelas clathrodes* sponges have afforded clathramides A (**112**), B (**113**), C (**114**), and D (**115**).[104,118]



95 R = Br (midpacamide)
96 R = H

97 (keramadine)

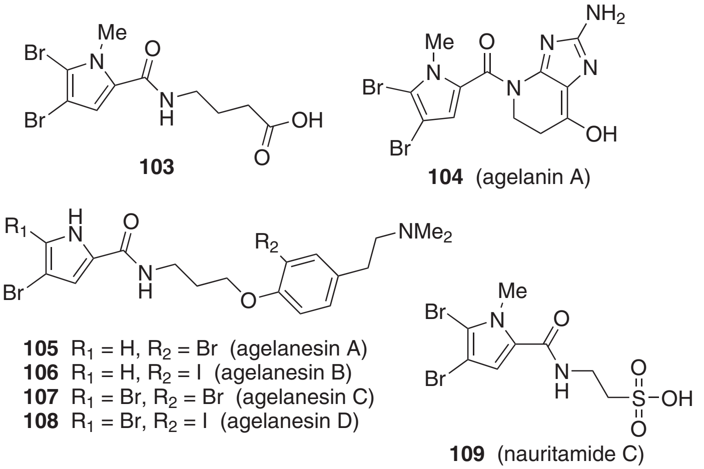
98 (hymenidin)

99 (manzacidin A)

100 R = OH (manzacidin B)
101 R = H (manzacidin C)

102 (mauritamide A)

Figure 13 Bromopyrrole alkaloids **95–102**.



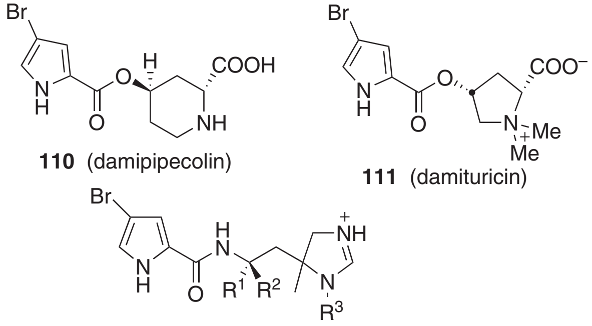
103

104 (agelanin A)

105 R_1 = H, R_2 = Br (agelanesin A)
106 R_1 = H, R_2 = I (agelanesin B)
107 R_1 = Br, R_2 = Br (agelanesin C)
108 R_1 = Br, R_2 = I (agelanesin D)

109 (nauritamide C)

Figure 14 Bromopyrrole alkaloids **103–109**.

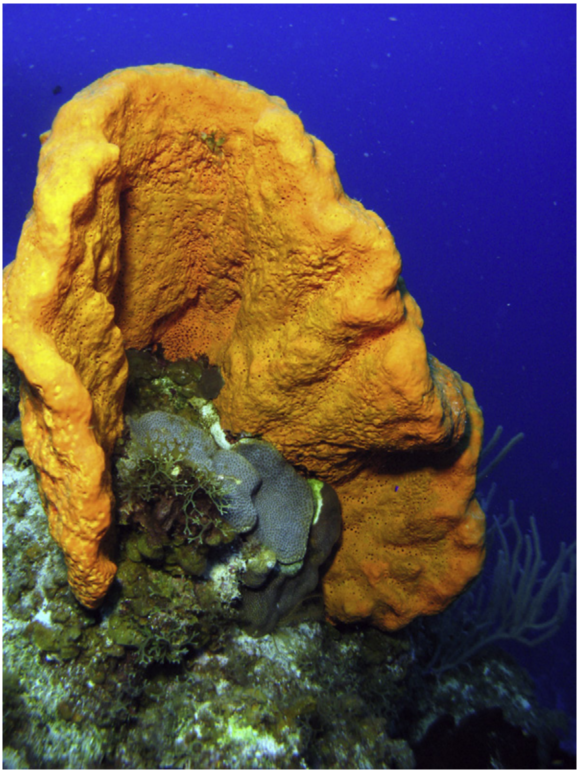


110 (damipipecolin)

111 (damituricin)

112 $R^1 = H, R^2 = CO_2^-, R^3 = Me$ (clathramide A)
113 $R^1 = CO_2^-, R^2 = H, R^3 = Me$ (clathramide B)
114 $R^1 = H, R^2 = CO_2^-, R^3 = H$ (clathramide C)
115 $R^1 = CO_2^-, R^2 = H, R^3 = H$ (clathramide D)

Figure 15 Bromopyrrole alkaloids **110–115**.



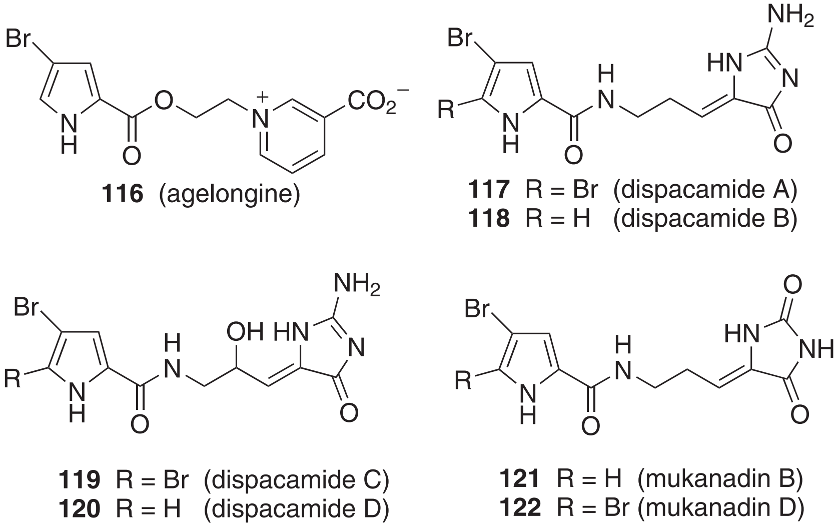
Agelas clathrodes A common marine sponge that produces the clathramides **112–115**.

Photo 2: Professor Joseph R. Pawlik.

Agelongine (**116**) is found in *Agelas longissima*, [119] a sponge that along with *A. conifera*, *A. clathrodes*, and *A. dispar* contains dispacamide A (**117**), B (**118**), C (**119**), and D (**120**)[120,121] (Figure 16). This latter alkaloid was isolated as "mukanadin A" along with the new mukanadin B (**121**) from *Agelas nakamurai*.[106] Both **121** and mukanadin D (**122**) were found in the Jamaican sponge *Didiscus oxeata*.[122]

The first example of an antifouling spermidine alkaloid is pseudoceratidine (**123**) found in the Japanese sponge *Pseudoceratina purpurea*[123] (Figure 17). The Okinawan *Hymeniacidon* sp. produces tauroacidins A (**124**, **125**) and B (**126**, **127**), which possess tyrosine kinase activity.[124] The structurally related taurodispacamide A (**128**) is present in *Agelas oroides* from the Mediterranean.[125] The Floridian *Agelas wiedenmayeri* has furnished **129**, which may be a biosynthetic precursor to hymenidin (**98**) and oroidin (**69**) alkaloids.[126] Laughine (**130**) was characterized in the Dominican sponge *Eurypon laughlini*.[127]

Both arginine (**131**) and lysine (**132**) analogs of **129** are present in the Bahamanian sponge *Stylissa caribica*[128] (Figure 18). Another Bahamanian sponge, *Agelas sventres*, contains sventrin (**133**) (*N*-methyloroidin), which is a feeding deterrent to reef fish.[129] The bromopyrrole alkaloids **134–136** are present in the Corsican sponge *Axinella verrucosa*.[100]



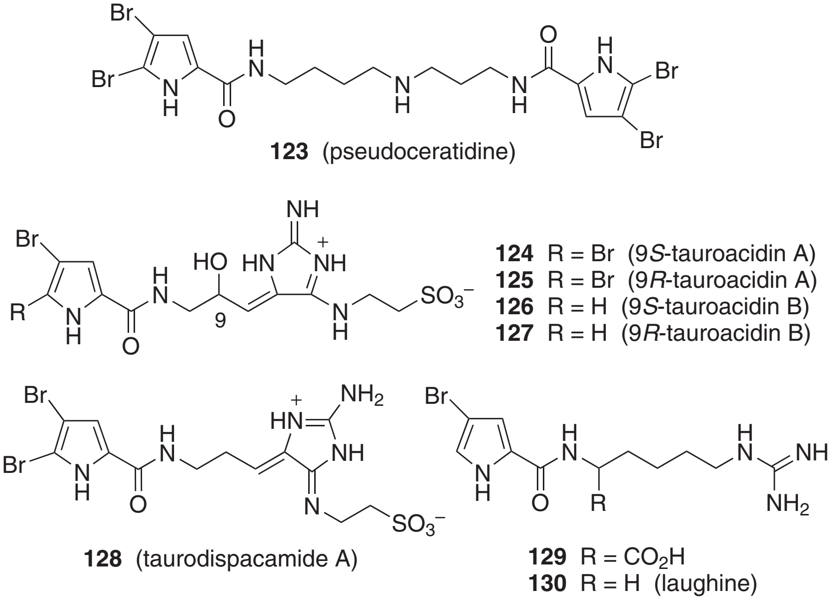
116 (agelongine)

117 R = Br (dispacamide A)
118 R = H (dispacamide B)

119 R = Br (dispacamide C)
120 R = H (dispacamide D)

121 R = H (mukanadin B)
122 R = Br (mukanadin D)

Figure 16 Bromopyrrole alkaloids **116–122**.



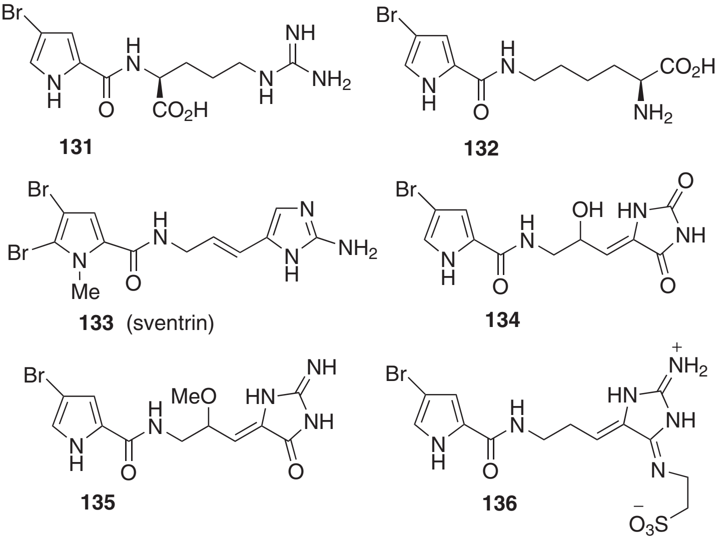
123 (pseudoceratidine)

124 R = Br (9*S*-tauroacidin A)
125 R = Br (9*R*-tauroacidin A)
126 R = H (9*S*-tauroacidin B)
127 R = H (9*R*-tauroacidin B)

128 (taurodispacamide A)

129 R = CO_2H
130 R = H (laughine)

Figure 17 Bromopyrrole alkaloids **123–130**.



131

132

133 (sventrin)

134

135

136

Figure 18 Bromopyrrole alkaloids **131–136**.

Agelas sventres A marine sponge that produces sventrin **133**.

Photo 3: Professor Joseph R. Pawlik.

Probably, the first halopyrrole alkaloid to be isolated was dibromophakellin (**137**) and, subsequently, bromophakellin (**138**) from the Great Barrier Reef sponge *Phakellia flabellata*[130,131] (Figure 19). Dibromoisophakellin (**139**) is present in *Acanthella carteri*.[132] The related hymenialdisine (**140**) is found in several sponges: *Axinella verrucosa*, *Acanthella aurantiaca*,[133,134] *Hymeniacidon aldis*,[135] *Acanthella carteri*,[136] and *Hymeniacidon* sp. and *Axinella* sp.[137] The latter sponge contains axinohydantoin (**141**),[137] and hymenin (**142**) is found in *Hymeniacidon* sp. from Okinawa.[138] Stevensine (**143**) was first found in an unidentified sponge[139] and later in *Teichaxinella morchella* and *Ptilocaulis walpersi*.[140] The simple 2-bromoaldisin (**144**) has been isolated from *Hymeniacidon aldis* (Guam), *Lissodendoryx* sp. (Sri Lanka),[99] and *Phacellia fusca* (South China Sea).[141]

Newer examples of the hymenialdisine bromopyrrole family include 3-bromohymenialdisine (**145**) (*Axinella carteri*),[142] (*E*)-hymenialdisine (**146**) (*Stylotella aurantium*),[143] (*Z*)-axinohydantoin (**147**) (*Stylotella aurantium*),[144] and spongiacidins A (**148**) and B (**149**) (*Hymeniacidon*

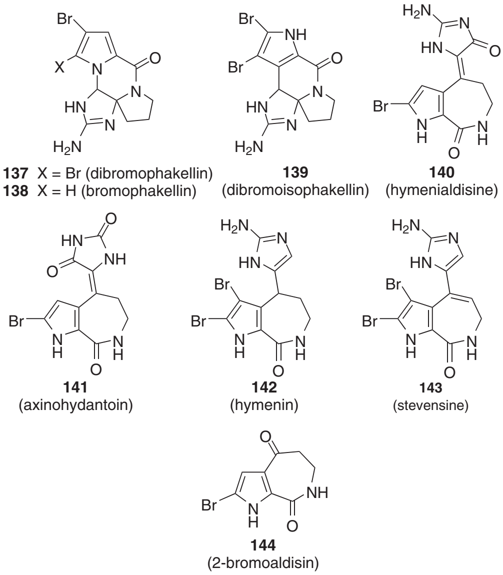
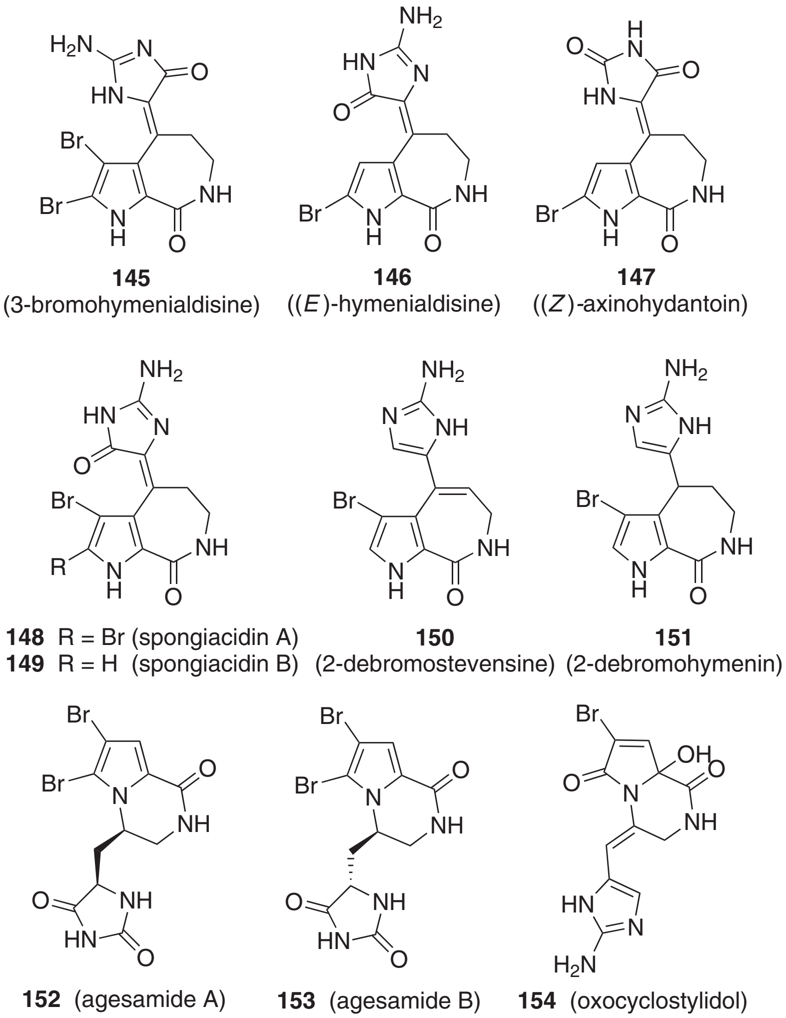


Figure 19 Brominated phakellins and related pyrrole lactam alkaloids **137–144**.

Axinella corrugata, **a sponge containing bromopyrrole alkaloid stevensine (143).**
Photo 4: Professor Joseph R. Pawlik.

sp.)[145] (Figure 20). "Spongiacidin D" is the same as **147**, and **148** is the (*E*)-diastereomer of **145**. The Indonesian *Stylissa carteri* has provided 2-debromostevensine (**150**) and 2-debromohymenin (**151**).[146] The latter compound is chiral and has the same relative configuration as hymenin (**142**), but their absolute configuration remains to be established. An Okinawan *Agelas* sp. contains agesamides A (**152**) and B (**153**), of unknown absolute configurations.[147] The Bahamanian *Stylissa caribica* is home to oxocyclostylidol (**154**), which is optically active but of unknown absolute configuration.[148]


145 (3-bromohymenialdisine) **146** ((*E*)-hymenialdisine) **147** ((*Z*)-axinohydantoin)

148 R = Br (spongiacidin A)
149 R = H (spongiacidin B)
150 (2-debromostevensine) **151** (2-debromohymenin)

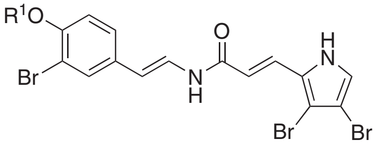
152 (agesamide A) **153** (agesamide B) **154** (oxocyclostylidol)

Figure 20 Bromopyrrole alkaloids **145–154**.

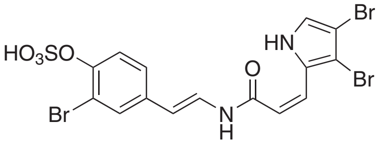
The marine ciliate *Pseudokeronopsis riccii* contains the novel keronopsamides A–C (**155–157**)[149] (Figure 21). The new 3-bromoaldisin (**158**) and 2,3-dibromoaldisin (**159**) are found in *Axinella damicornis* and *Stylissa flabelliformis*.[95]

Cyclooroidin (**160**) is present in *Agelas oroides*,[125] the structure of which was confirmed by synthesis including absolute configuration.[150] The Philippine *Axinella carteri* contains ugibohlin (**161**)[151] (Figure 22). Numerous more highly congested bromopyrrole alkaloids are known, such as dibromoagelasporin (**162**) from *Agelas* sp.,[152] and agelastatin A (**163**) and dibrominated compound **164** from a Coral Sea *Agelas dendromorpha* sponge.[153] The absolute configuration of agelastatin A has been determined by X-ray crystallography.[154] Agelastatins C (**165**) and D (**166**) were isolated from the Indian Ocean sponge *Cymbastela* sp.[155] The absolute configurations are as shown. The New Caledonian *Agelas dendromorpha* contains agelastatins E (**167**) and F (**168**).[156]

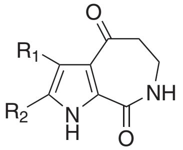
The interesting alkaloid ageladine A (**169**) occurs in the sponge *Agelas nakamurai* and is a potent inhibitor of matrix metalloproteinases[157] (Figure 23). An Okinawan *Agelas* sp. has afforded 9,10-dihydrokeramadine (**170**).[158] A Japanese sponge, *Axinella brevistyla*, contains the simple maleimides **171** and **172**, and *N*-methylmanzacidin C (**173**).[159] Another Okinawan *Agelas* sp. produces agelasine G (**174**).[160]



155 (keronopsamide A) R^1 = H
156 (keronopsamide B) R^1 = SO_3H

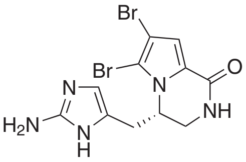


157 (keronopsamide C)

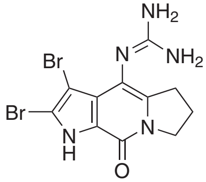


158 R_1 = Br, R_2 = H (3-bromoaldisin)
159 R_1 = R_2 = Br (2,3-dibromoaldisin)

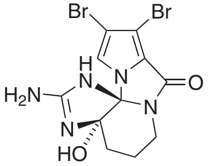
Figure 21 Keronopsamides **155–157** and bromopyrrole alkaloids **158–159**.



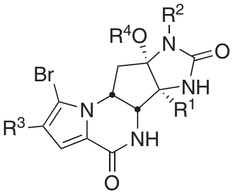
160 (*S*-cyclooroidin)



161 (ugibohlin)

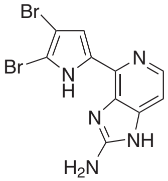


162

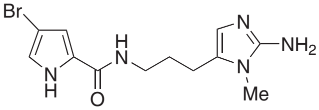


	R^1	R^2	R^3	R^4	
163	H	Me	H	H	(agelastatin A)
164	H	Me	Br	H	(agelastatin B)
165	OH	Me	H	H	(agelastatin C)
166	H	H	H	H	(agelastatin D)
167	H	Me	H	Me	(agelastatin E)
168	H	H	Br	H	(agelastatin F)

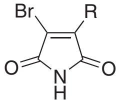
Figure 22 Agelastatins and related bromopyrrole alkaloids **160–168**.



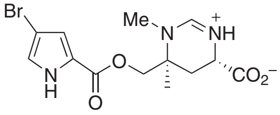
169 (ageladine A)



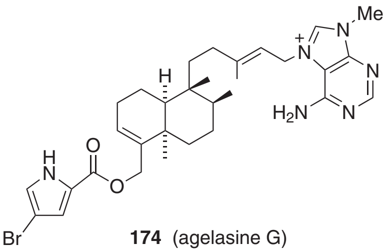
170 (9,10-dihydrokeramadine)



171 R = H
172 R = Br

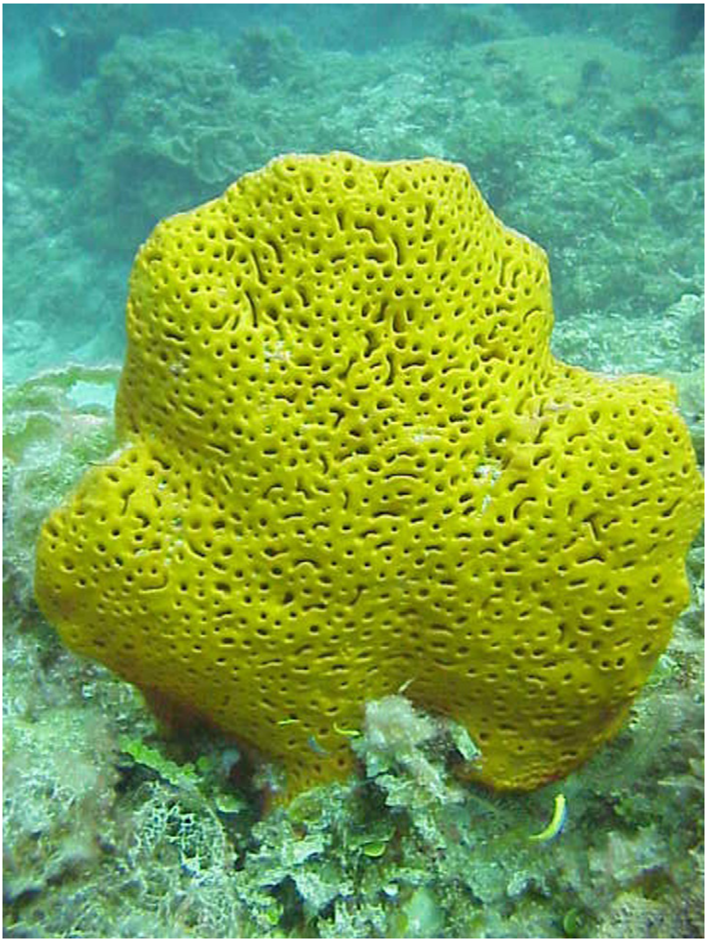


173 (*N*-methylmanzacidin C)



174 (agelasine G)

Figure 23 Bromopyrrole alkaloids **169–174**.

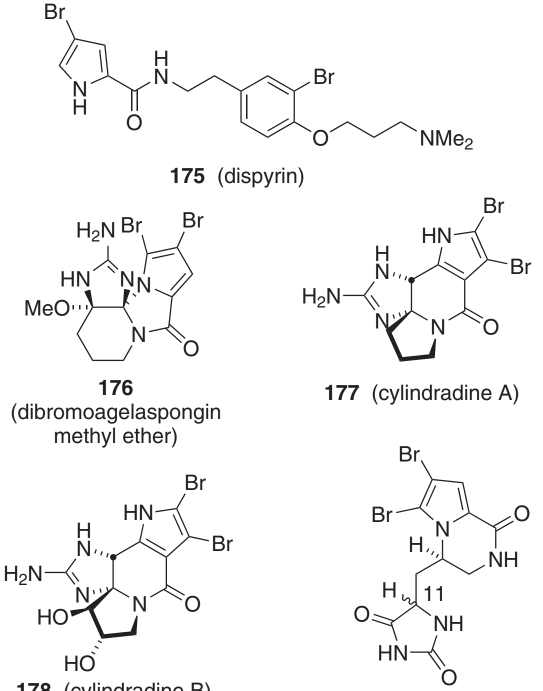


Agelas sp. An example of a very common marine sponge that produces a wide variety of halogenated alkaloids.

Photo 5: Professor Joseph R. Pawlik.

The Caribbean *Agelas dispar* has furnished the bromopyrrole dispyrin (**175**), which could have been included in the tyrosine section and dibromoagelaspongin methyl ether (**176**)[161] (Figure 24). The latter may well be an artifact from dibromoagelaspongin, which was also found in this sponge. Cylindradines A (**177**) and B (**178**) were isolated from *Axinella cylindratus*,[162] and the epimeric agesamides A (**179**) and B (**180**) are found in an Okinawan *Agelas* sp.[147]

The prolific Indonesian sponge *Stylissa carteri* produces latonduines A (**181**) and B (**182**). Their structures were confirmed by total synthesis[163]



175 (dispyrin)

176 (dibromoagelaspongin methyl ether)

177 (cylindradine A)

178 (cylindradine B)

179 α-$C_{11}H$ (agesamide A)
180 β-$C_{11}H$ (agesamide B)

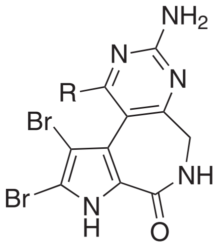
Figure 24 Bromopyrrole alkaloids **175–180**.

(Figure 25). Dibromophakellstatin (**183**) was isolated from *Phakellia mauritiana*,[164] and *Stylissa caribica* contains *N*-methyldibromoisophakellin (**184**), an excellent antifeedant.[165] The related monobromoisophakellin (**185**) is found in a Bahamian *Agelas* sp. sponge.[166] Brominated phakellin alkaloids **186** and **187–188** were isolated from *Axinella brevistyla*[159] and a Papua New Guinean *Agelas* sp. sponge,[167] respectively.

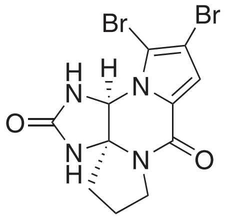
Slagenins A–C (**189–191**) were isolated from the Okinawan *Agelas nakamurai*,[168] and the absolute configurations were established by total synthesis[169] (Figure 26).

A series of nagelamides A–H, J–N (**192–204**) has been identified in an Okinawan *Agelas* sp.[158,170–172] (Figures 27–29).

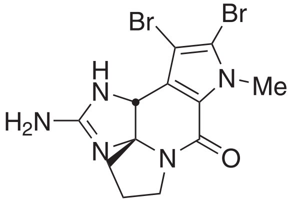
The first in a series of dimeric bromopyrrole alkaloids was isolated from *Agelas sceptrum* in the form of the optically active sceptrin (**205**)[173] (Figure 30). This was followed by the characterization of **206–209** from *Agelas conifera*.[174] This latter investigation uncovered the ageliferins **210–212**, [174,175] which are related to the nagelamides E–G (**196–198**).



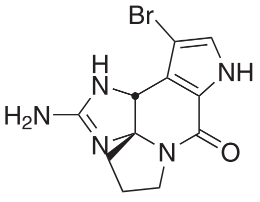
181 R = H (latonduine A)
182 R = CO_2H (latonduine B)



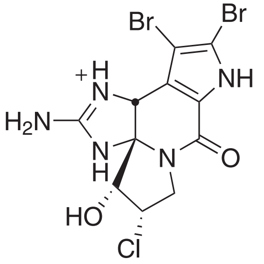
183 (dibromophakellstatin)



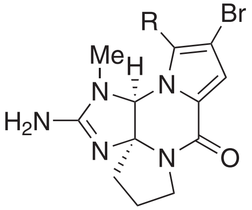
184
(*N*-methyldibromoisophakellin)



185
(monobromoisophakellin)

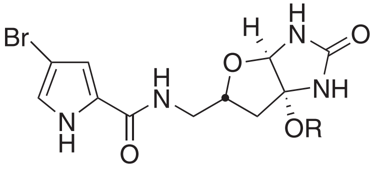


186

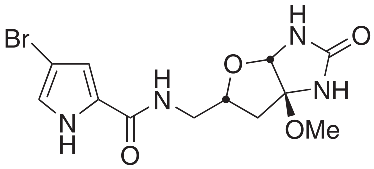


187 R = Br
188 R = H

Figure 25 Bromopyrrole alkaloids **181–188**.

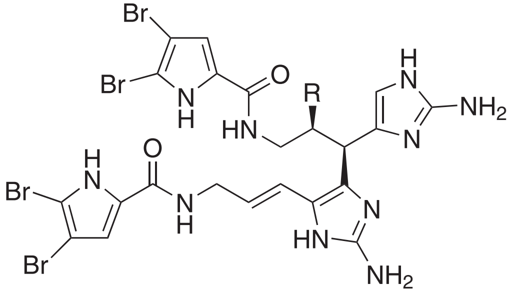


189 R = H (slagenin A)
190 R = Me (slagenin B)

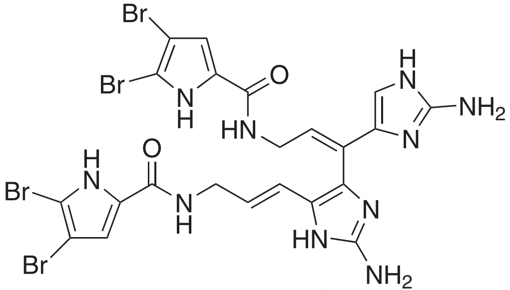


191 (slagenin C)

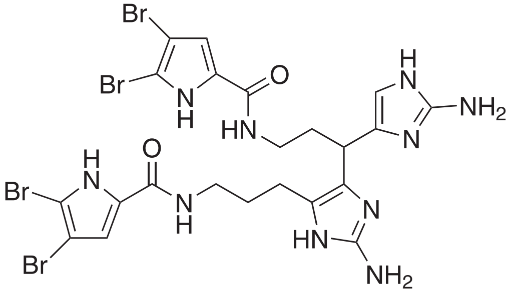
Figure 26 Bromopyrrole slagenin alkaloids **189–191**.



192 R = H (nagelamide A)
193 R = OH (nagelamide B)



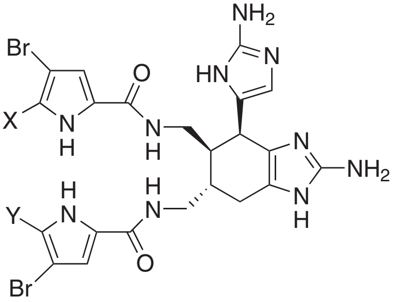
194 (nagelamide C)



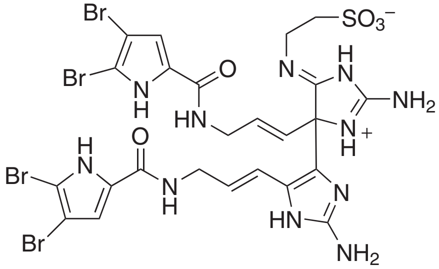
195 (nagelamide D)

Figure 27 Bromopyrrole nagelamide alkaloids **192**–**195**.

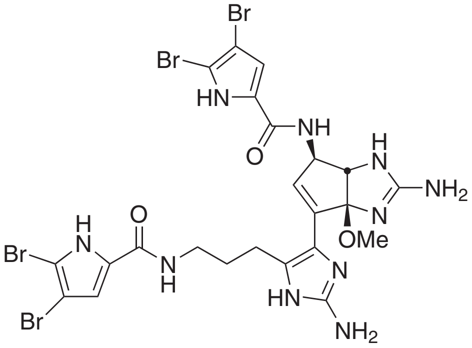
The Pohnpei sponge *Astrosclera willeyana* has afforded the new *N*-methylageliferins **213**–**219**,[176] and the similar nakamuric acid (**220**) was found in the Indonesian *Agelas nakamurai*[177] (Figure 31). Bromosceptrin (**221**) was identified in the Florida sponge *Agelas conifera*,[178] and aromatic benzosceptrins B (**222**) and C (**223**) were discovered in several sponges: *Agelas* cf. *mauritiana* (Guadalcanal),[179] *Phakellia* sp. (New Caladonia),[179] *Agelas dendromorpha* (New Caledonia),[156] and *Agelas* sp. (Okinawa).[180]



196 X = Y = H (nagelamide E)
197 X = Br, Y = H (nagelamide F)
198 X = Y = Br (nagelamide G)



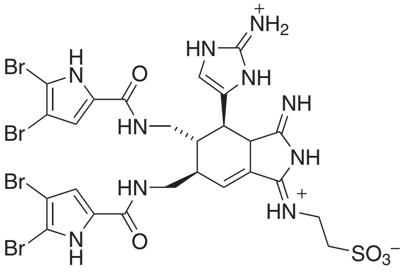
199 (nagelamide H)



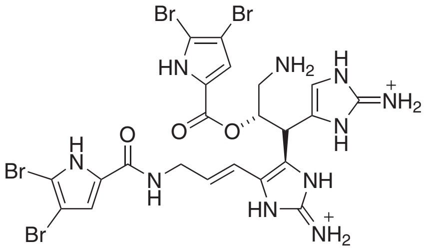
200 (nagelamide J)

Figure 28 Bromopyrrole nagelamide alkaloids **196**–**200**.

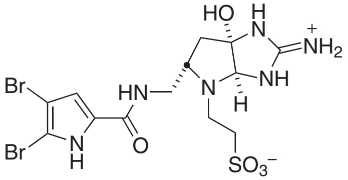
The oroidin dimer mauritiamine (**224**) was found in a Japanese *Agelas mauritiana*[181] (Figure 32). A different set of pyrrole dimers are the tambjamines B (**225**) and D (**226**), which are present in the bryozoan *Sessibugula translucens*.[182] Interestingly, these alkaloids are found in the predatory



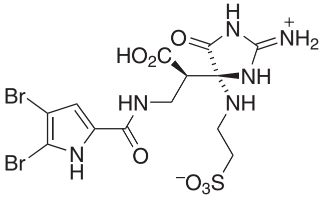
201 (nagelamide K)



202 (nagelamide L)



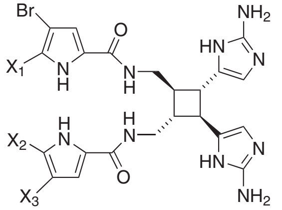
203 (nagelamide M)



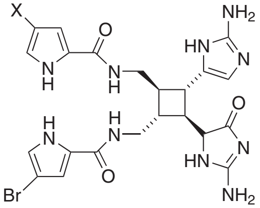
204 (nagelamide N)

Figure 29 Bromopyrrole nagelamide alkaloids **201–204**.

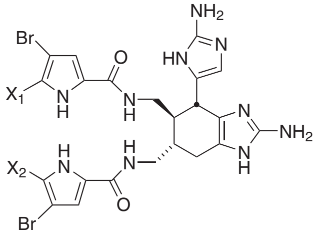
nudibranchs *Tambje eliora* and *T. abdere*, which feed on *S. translucens*, and are also present in the carnivorous nudibranch *Roboastra tigris*, which in turn preys on *Tambje*.[182,183] The Tasmanian bryozoan *Bugula dentata* has yielded tambjamines G–J (**227–230**).[184] The sodium sulfamate **231** of 2,3,4-tribromopyrrole (**68**) was isolated from the marine worm *Saccoglossus kowalevskii*[185] and may serve as the precursor to **68**.



205 $X_1 = X_2 = H, X_3 = Br$ (sceptrin)
206 $X_1 = X_2 = X_3 = H$
207 $X_1 = X_2 = X_3 = Br$

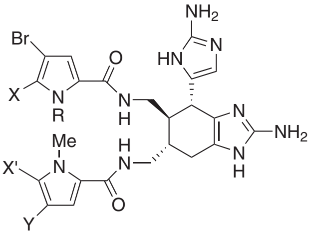


208 X = H
209 X = Br

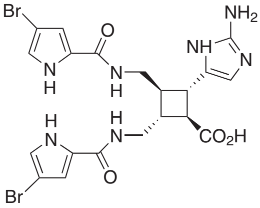


210 $X_1 = X_2 = H$ (ageliferin)
211 $X_1 = Br, X_2 = H$
212 $X_1 = X_2 = Br$

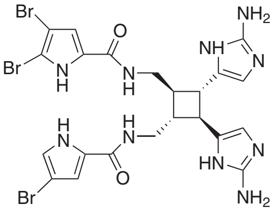
Figure 30 Bromopyrrole sceptrin and related alkaloids **205–212**.



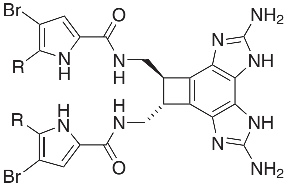
213 R = X = X' = H, Y = Br
214 R = Me, X = X' = H, Y = Br
215 R = X = Y = H, X' = Br
216 R = Me, X = Y = H, X' = Br
217 R = X' = H, X = Y = Br
218 R = X = H, X' = Y = Br
219 R = H, X = X' = Y = Br



220 R = H (nakamuric acid)



221 (bromosceptrin)



222 (benzosceptrin B) R = H
223 (benzosceptrin C) R = Br

Figure 31 Bromopyrrole dimeric alkaloids **213–223**.

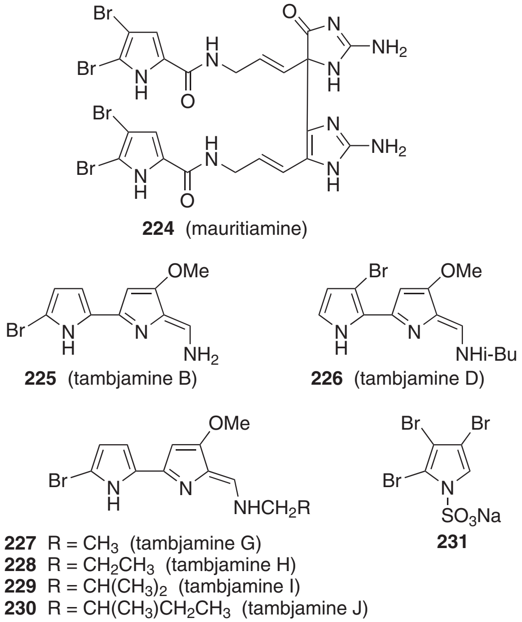


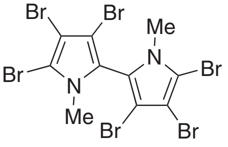
Figure 32 Bromopyrrole alkaloids **224**–**231**.

Reticulida fungia, **a typical nudibranch.**

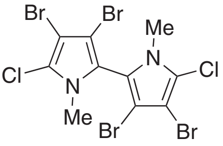
Photo 6: Professor Junichi Tanaka.

Several new analogs of polybrominated 2,2′-bipyrrole **67** were identified in seabird eggs, [186] **232** and **233**, which were established by synthesis[187] and X-ray crystallography[188] (Figure 33). At least six other mixed bromochloro-2,2′-bipyrroles are ubiquitous in the marine environment (zooplankton, fish, seabirds, seal, porpoise, dolphin, whale, etc.) but have not been characterized.[189–192] It is presumed that these alkaloids have a marine bacteria origin. Given their resemblance to anthropogenic polychlorinated biphenyls, it is not surprising that the polyhalogenated bipyrroles are widespread in the food web. The related polychlorinated 1,2′-bipyrrole Q1 (**234**), the structure of which was established by synthesis, [193,194] is even more prevalent in the environment than the 2,2′-bipyrrole counterparts.[195–199] Q1 and mixed bromo–chloro analogs are found in humans who consume whale blubber,[196] in the liver of the tiger shark,[200] and in an expanding range of marine organisms.[199, 201,202] At least 25 polyhalogenated 1,2′-bipyrrole alkaloids are known, but they have not yet been individually characterized. It is noteworthy that Q1 and several brominated Q1 analogs were discovered in archived whale oil from a 1921 voyage of the whaling ship *Charles W. Morgan*. This oil was not found to contain PCBs, DDT, or DDE.[203] Moreover, radiocarbon analysis of Q1 (**234**) and **233** reveals a natural origin and not a petroleum origin.[204]

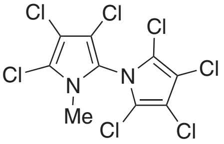
A series of chlorinated pyrrole-fatty acid alkaloids are known (Figure 34). Rumbrin (**235**) is found in the fungus *Auxarthron umbrinum* and prevents membrane lipid peroxidation and calcium overload.[205,206] Likewise, thiazohalostatin (**236**) from cultures of *Actinomadura* sp. has a cytoprotective effect.[207,208] The relative stereochemistry of the four stereocenters was not determined. The marine ciliate *Pseudokeronopsis rubra* contains keronopsins A_1 (**237**), A_2 (**238**), B_1 (**239**), and B_2 (**240**).[209]



232

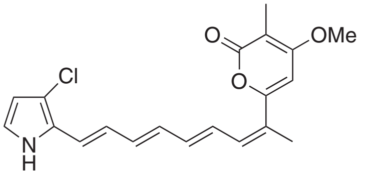


233

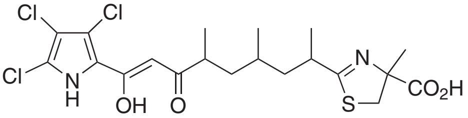


234 (Q1)

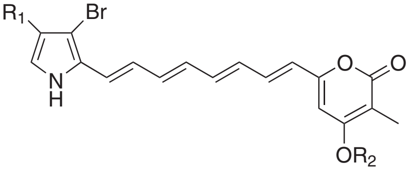
Figure 33 Halogenated bipyrrole alkaloids **232–234**.



235 (rumbrin)



236 (thiazohalostatin)



237 R_1 = H, R_2 = SO_3Na (keronopsin A_1)
238 R_1 = Br, R_2 = SO_3Na (keronopsin A_2)
239 R_1 = R_2 = H (keronopsin B_1)
240 R_1 = Br, R_2 = H (keronopsin B_2)

Figure 34 Halogenated pyrrole alkaloids **235–240**.

The Australian soil fungus *Gymnoascus reessii* has afforded 12*E*-isorumbrin (**241**)[210] (Figure 35). The related auxarconjugatins A, B, and (3′*Z*)-A (**242–244**) were isolated from the Arizonian soil microbe *Auxarthron conjugatum*,[211] and a New Zealand forest fungus, *Chamonixia pachydermis*, has afforded pachydermin (**245**).[212]

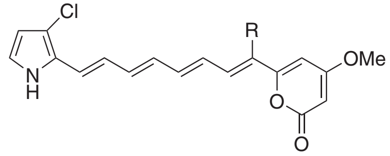
Malbranpyrroles C–F (**246–249**) were found in the thermophilic *Malbranchea sulfurea* fungus in a Taiwan fumarole[213] (Figure 36).

The novel phorbazoles A–D (**250–253**) were found in the sponge *Phorbas aff. clathrata*[214] (Figure 37). The novel chromeno[2,3-*b*] pyrrole TAN-876A (**254**) along with TAN-876B (**255**) are produced by a *Streptomyces* sp., and both alkaloids exhibit strong antibacterial activity[215].

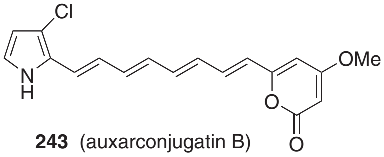
Fermentation cultures of *Microtetraspora* (*Actinomadura spiralis*) afford pyralomicins **256–262**[216–219], and cultures of *Streptomyces armeniacus* and *S. rimosus* furnish streptopyrroles **263–269**[220,221] (Figure 38).

The two nitropyrrolins C (**270**) and E (**271**) were isolated from a marine *Streptomycetaceae*[222] (Figure 39).

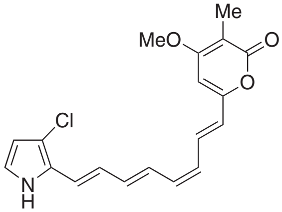
A deep-sea sediment (possibly *Streptomyces*) has afforded the novel 1,3′-bipyrroles, marinopyrroles A–F (**272–277**), which exist as



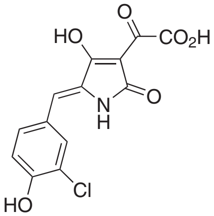
241 R = Me ((12*E*)-isorumbrin)
242 R = H (auxarconjugatin A)



243 (auxarconjugatin B)

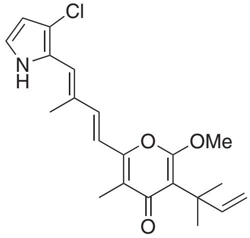


244 (3'-*cis*-auxarconjugatin A)

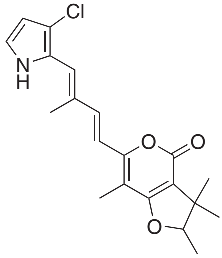


245 (pachydermin)

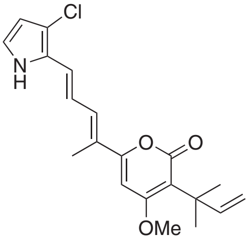
Figure 35 Chloropyrrole alkaloids **241–245**.



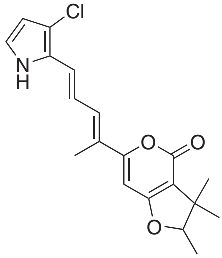
246 (malbranpyrrole C)



247 (malbranpyrrole D)

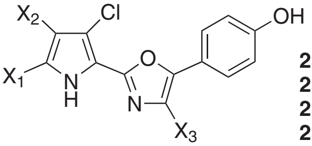


248 (malbranpyrrole E)

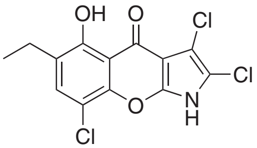


249 (malbranpyrrole F)

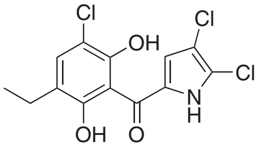
Figure 36 Chlorinated malbranpyrrole alkaloids **246–249**.



250 $X_2 = X_3 = Cl, X_1 = H$ (phorbazole A)
251 $X_1 = X_2 = Cl, X_3 = H$ (phorbazole B)
252 $X_2 = Cl, X_1 = X_3 = H$ (phorbazole C)
253 $X_1 = X_2 = X_3 = H$ (phorbazole D)

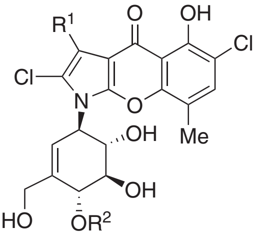


254 (TAN-876 A)

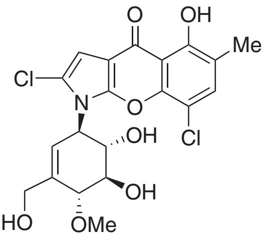


255 (TAN-876 B)

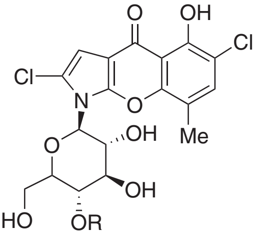
Figure 37 Chloropyrrole alkaloids **250**–**255**.



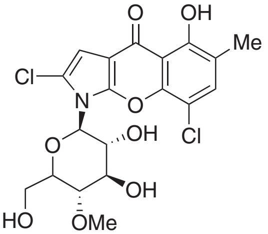
256 $R^1 = H, R^2 = Me$ (pyralomicin 1a)
257 $R^1 = R^2 = H$ (pyralomicin 1c)
258 $R^1 = Cl, R^2 = H$ (pyralomicin 1d)



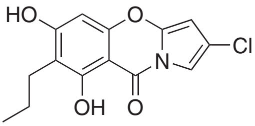
259 (pyralomicin 1b)



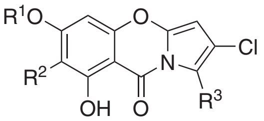
260 R = Me (pyralomicin 2a)
261 R = H (pyralomicin 2c)



262 (pyralomicin 2b)

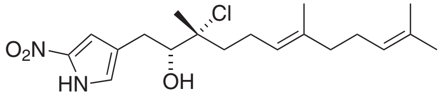


263 (streptopyrrole)

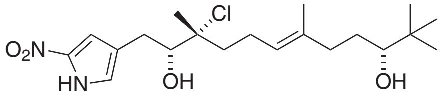


264 $R^1 = R^3 = H, R^2 = Et$
265 $R^1 = H, R^2 = Pr, R^3 = Cl$
266 $R^1 = Me, R^2 = Pr, R^3 = H$
267 $R^1 = R^3 = H, R^2 = Bu$
268 $R^1 = Me, R^2 = Et, R^3 = H$
269 $R^1 = Me, R^2 = Pr, R^3 = Cl$

Figure 38 Chlorinated pyralomicins and related alkaloids **256**–**269**.

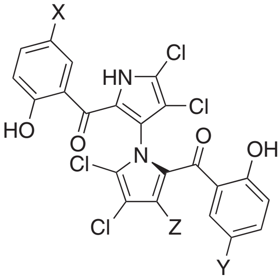


270 (nitropyrrolin C)

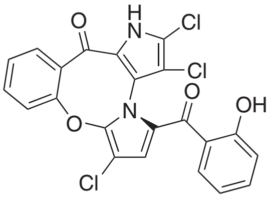


271 (nitropyrrolin E)

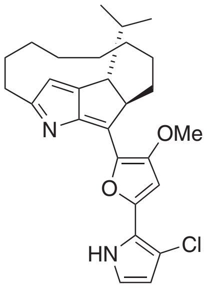
Figure 39 Chlorinated nitropyrrolin alkaloids **270–271**.



272 (marinopyrrole A) X = H, Y = H, Z = H
272 (marinopyrrole B) X = H, Y = H, Z = Br
274 (marinopyrrole C) X = Cl, Y = H, Z = H
275 (marinopyrrole D) X = H, Y = Cl, Z = H
276 (marinopyrrole E) X = H, Y = Br, Z = H



277 (marinopyrrole F)

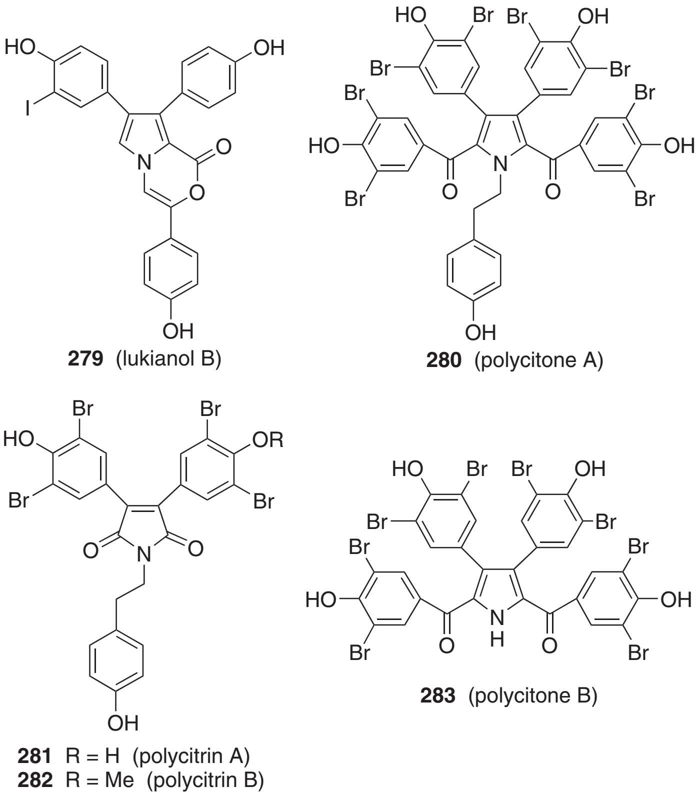


278 (roseophilin)

Figure 40 Chlorinated marinopyrroles and roseophilin **272–278**.

optically active atropoenantiomers (except for **278**), [223,224] similar to the case of 5,5′-dichloro-1,1′-dimethyl-3,3′,4,4′-tetrabromo-2,2′-bipyrrole (**233**)[225] (Figure 40). Roseophilin (**278**) from *Streptomyces griseoviridis* shows significant cytotoxicity against human cancer cell lines,[226] and its absolute configuration has been determined.[227]

Iodine-containing pyrroles are rare in nature, but lukianol B (**279**) was found in a tunicate[228] (Figure 41). Polycitone A (**280**) and polycitrins A (**281**) and B (**282**) are found in a *Polycitor* sp. ascidian, [229] and polycitone B (**283**) is found in the Madagascan *Polycitor africans*.[230]



279 (lukianol B)

280 (polycitone A)

281 R = H (polycitrin A)
282 R = Me (polycitrin B)

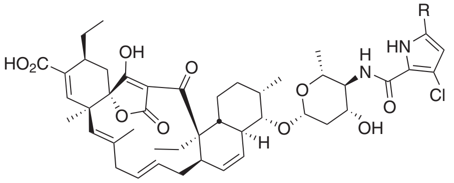
283 (polycitone B)

Figure 41 Halogenated pyrrole alkaloids **279–283**.

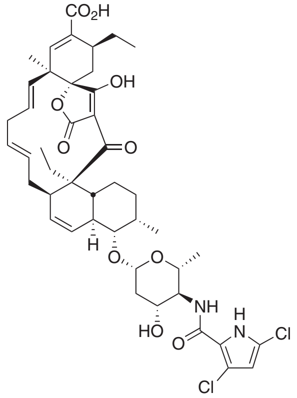
The *Actinoma* sp. metabolites decatromicins A (**284**) and B (**285**) are active against methicillin-resistant *Staphylococcus aureus*[231,232] and are structurally related to pyrrolosporin A (**286**)[233,234] (Figure 42).

This section concludes with a presentation of a set of stunningly complex marine pyrrole alkaloids that have captivated the synthetic community for the past decade. Stylissadines A (**287**) and B (**288**) were isolated from the Bahamian sponge *Stylissa caribica*[235] and appear to be dimers of massadine (**293**) (*vide infra*) (Figure 43). The Australian *Stylissa flabellata* also contains **287** and **288** (named as "flabellazoles" A and B).[236] Their absolute stereochemistry was assigned from CD measurements.[236]

Another Australian sponge, *Axinella* sp., has afforded axinellamines A–D (**289–292**),[237] which are similar to massadine (**293**) from the Japanese sponge *Stylissa* aff. *massa*[238] (Figure 44). Many of these 2-aminoimidazole alkaloids are isolated as acid salts (e.g., trifluoroacetates). Massadine chloride (**294**), a possible biosynthetic precursor to **293**, has been isolated from the Caribbean *Stylissa caribica*.[239]

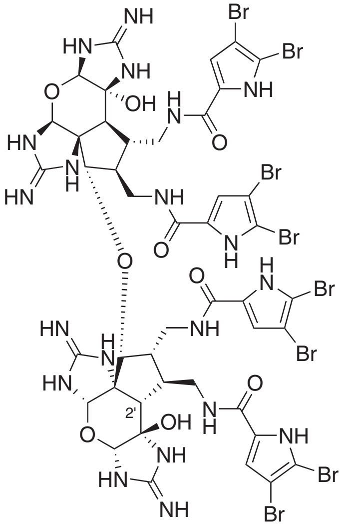


284 R = H (decatromicin A)
285 R = Cl (decatromicin B)



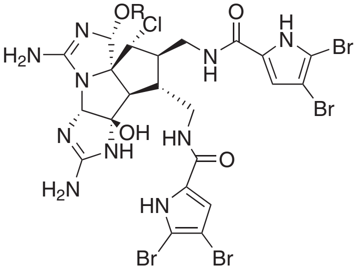
286 (pyrrolosporin A)

Figure 42 Chlorinated pyrrole alkaloids **284–286**.

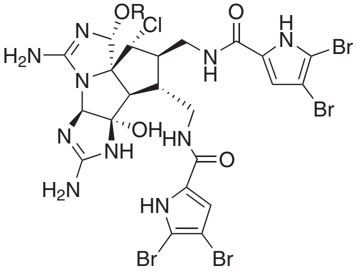


287 (stylissadine A) (C2'*S*)
288 (stylissadine B) (C2'*R*)

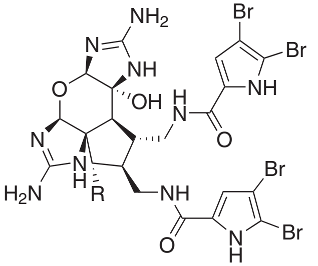
Figure 43 Brominated stylissadine alkaloids **287–288**.



289 R = H (axinellamine A)
290 R = Me (axinellamine C)



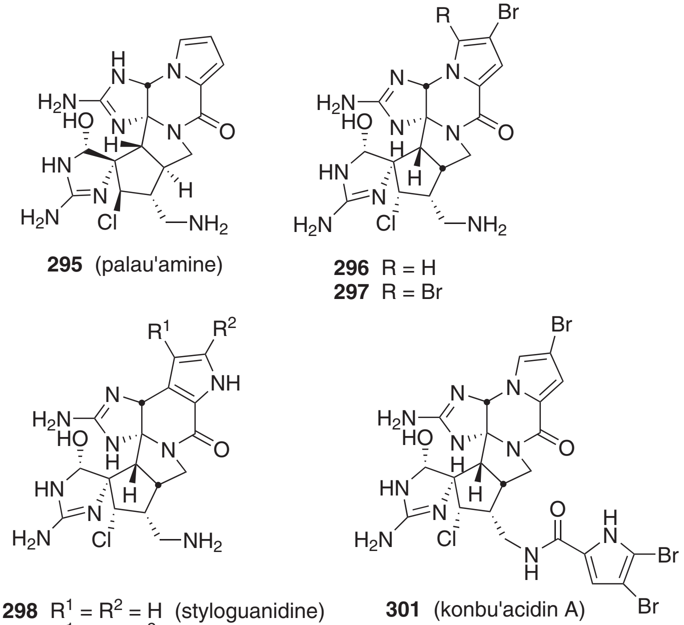
291 R = H (axinellamine B)
292 R = Me (axinellamine D)



293 R = H (massadine)
294 R = Cl (masssadine chloride)

Figure 44 Halogenated pyrrole alkaloids **289**–**294**.

Palau'amine (**295**), from the South Pacific *Stylotella agminata* (renamed as *Stylotella aurantium*), has captured the imagination of synthetic chemists since its discovery[240,241,834] (Figure 45). This sponge also contains 4-bromopalau'amine (**296**) and 4,5-dibromopalau'amine (**297**),[241] and, in a separate collection, styloguanidine (**298**), 3-bromostyloguanidine (**299**), and 2,3-dibromostyloguanidine (**300**), which are potent antifouling alkaloids.[242] These latter three compounds were also isolated as "isopalau'amines" from *Stylotella aurantium*.[241] The related alkaloid konbu'acidin A (**301**) was found in the Okinawan sponge *Hymeniacidon*.[243]



295 (palau'amine)

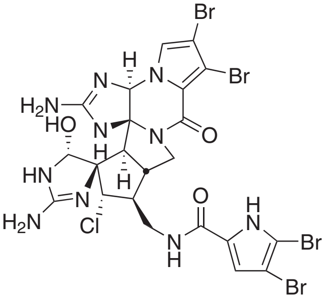
296 R = H
297 R = Br

298 $R^1 = R^2 = H$ (styloguanidine)
299 $R^1 = Br, R^2 = H$
300 $R^1 = R^2 = Br$

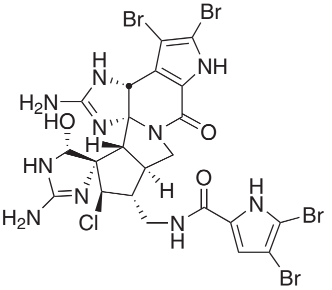
301 (konbu'acidin A)

Figure 45 Chlorinated palau'amine and related alkaloids **295**–**301**.

Stylotella aurantium, a sponge that produces palau'amine.
Photo 7: Dr. Andrew Flowers.



302 (konbu'acidin B)



303
(tetrabromostyloguanidine) (= carteramine A?)

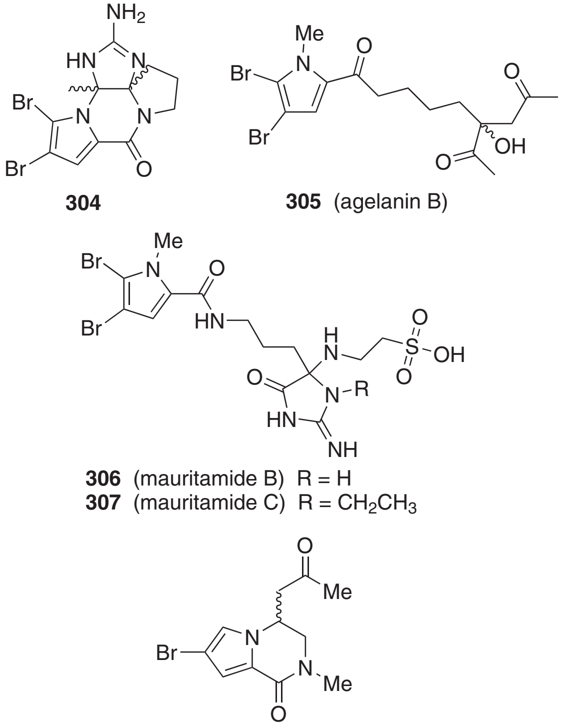
Figure 46 Halogenated pyrrole alkaloids **302**–**303**.

Konbu'acidin B (**302**) was characterized from the Australian sponge *Stylissa flabellata*,[236] and the Bahamaian *Stylissa caribica* contains tetrabromostyloguanidine (**303**)[244] (Figure 46). Several structural studies on these alkaloids led to the revision of three stereocenters[236,244–247] and the determination of the absolute configuration of palau'amine (**295**).[248] The magnificent total synthesis of this extraordinary alkaloid[249,250] is a fitting culmination to this section of complex halopyrrole alkaloids.

This pyrrole alkaloid section concludes with a more typical collection of halogenated pyrroles, **304**–**308**, from the newly identified *Agelas linnaei* sponge from Indonesia[116] (Figure 47).

C. Indoles

Nature has long understood what pharmaceutical chemists realize – indole is the preeminent heterocyclic ring system present in biologically active molecules. Furthermore, as we have seen with pyrrole, indole is extremely reactive in electrophilic halogenation. As a result, myriad natural haloindoles are known, from simple brominated indoles in marine worms to remarkably complex halogenated indoles in bryozoa.[251,252]



304

305 (agelanin B)

306 (mauritamide B) R = H
307 (mauritamide C) R = CH_2CH_3

308 (longamide C)

Figure 47 Bromopyrrole alkaloids **304–308**.

The ancient Egyptian dye, Tyrian Purple (6,6′-dibromoindigotin) (**309**), was isolated in 1909 from the mollusc *Murex brandaris*[253] and later from the sea snails *Purpura aperta* and *P. lapillus*[254] (Figure 48). Tyrian Purple was the focus of a major industry in the Mediterranean for >2500 years, and a rich history of this natural dye[255–267] and the chemical processes involved in its biogenesis have been presented,[268–279] and a bibliography is available.[280] Tyrian Purple was also an important dye in Central America and Western Mexico.[281–283] Interestingly, in contrast to the snails used in the Mediterranean to extract Tyrian Purple, the *Plicopurpura pansa* dye extraction involved "milking" without killing the snail.[282,283]

The biogenesis of Tyrian Purple is of enormous interest since the snail precursors are colorless. Several of these compounds have been isolated from molluscs, including indoxysulfates **310–311** and indoxyl **312** from *Dicathais orbita*[268] and **313** and **314** from *Murex trunculus*, *M. brandis*, *M. erinaceus*, and *Purpura haemastoma*.[269] Indoxyl **312** and thioacetal **315** are found in *Dicathais orbita*, *Mancinella bufo*, *M. keineri*, and *M. distinguenda* (=*M. ancinella*).[270,271] Cholines **310–311** are also present in *M. keineri*.[272] The immediate precursors

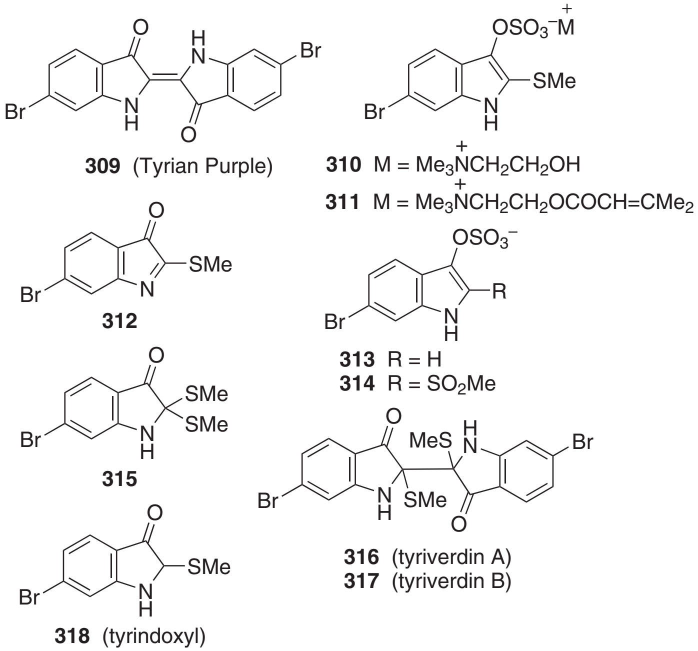


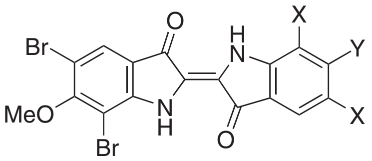
Figure 48 Tyrian Purple and related bromoindole alkaloids **309–318**.

of Tyrian Purple (**309**) are thought to be tyriverdins A (**316**) and B (**317**), which were isolated from *Nucella lapillus*[251] and *Thais clavigera*.[284] Chemical studies suggest that tyrindoxyl (**318**), generated from **310**/**311**, reacts with indoxyl **312** to afford the tyriverdins (**316**/**317**).[251,284–286] The relative stereochemistry of the diastereomeric tyriverdins A and B is unknown.

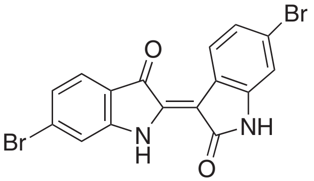
Perhaps from its diet, the marine acorn worm *Ptychoderma flava laysanica* contains Tyrian Purple (**309**) and two related alkaloids **319** and **320**[287] (Figure 49). Additional studies of the Tyrian Purple molluscs have discovered the new 6,6′-dibromoindirubin (**321**),[288] 6-bromoindigotin (**322**),[288,289] 6-bromoindirubin (**323**),[290] and 6′- bromoindirubin (**324**).[290] The novel antitumor chlorinated indigo glycosides akashins A–C (**325–327**) were found in cultures of a terrestrial *Streptomyces* sp.[291]

The Tyrian Purple molluscs have yielded several simple 6-bromoindoles, including 6-bromoisatin (**328**),[292,293] 6-bromoindoxyl (**329**),[293] sulfoxide **330**,[293] and methyl ether **331**[293] (Figure 50).

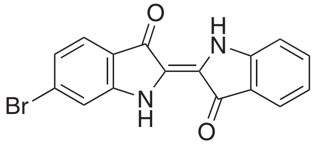
Marine acorn worms are a rich source of simple halogenated indoles (Figure 51). Thus, *Ptychodera flava laysanica* produces **332**,[287] **333**,[294] **334–336**,[295] **337–338**,[296] and another *Ptychodera* sp. from a deep Maui cave contains 3,4,6-tribromoindole (**339**),[297] which is also found in the worm *Glossobalanus carnosus*.[296] Another *Glossobalanus* sp. contains 3-bromoindole



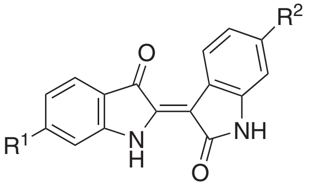
319 X = Br, Y = OMe
320 X = H, Y = Br



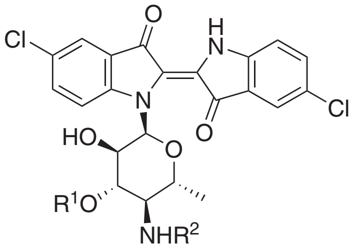
321 (6,6'-dibromoindirubin)



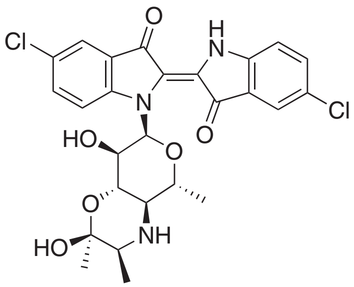
322 (6-bromoindigotin)



323 R^1 = H, R^2 = Br (6-bromoindirubin)
324 R^1 = Br, R^2 = H (6'-bromoindirubin)

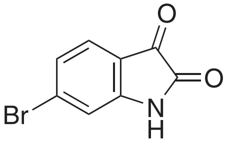


325 R^1 = R^2 = H (akashin A)
326 R^1 = H, R^2 = $COCH_3$ (akashin B)

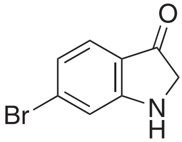


327 (akashin C)

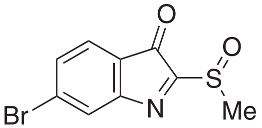
Figure 49 Halogenated biindole alkaloids **319**–**327**.



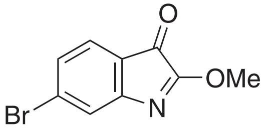
328



329



330



331

Figure 50 Bromoindole alkaloids **328**–**331**.

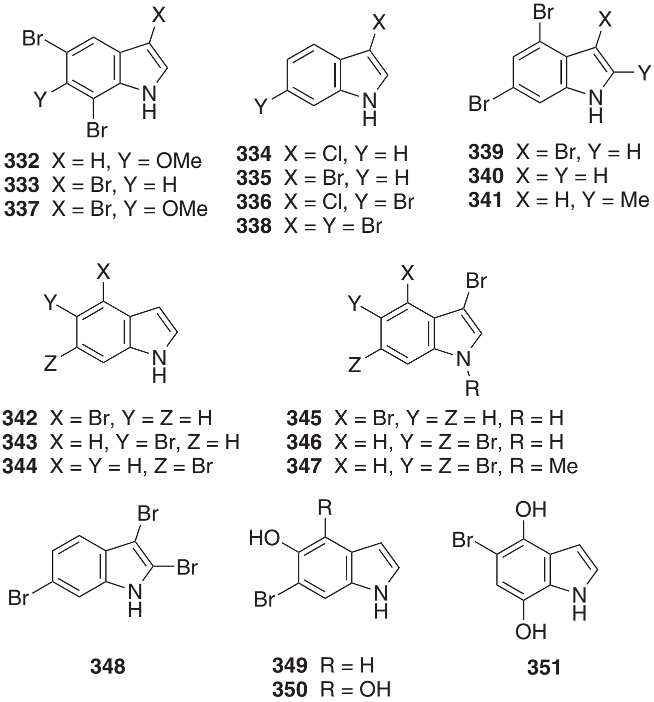
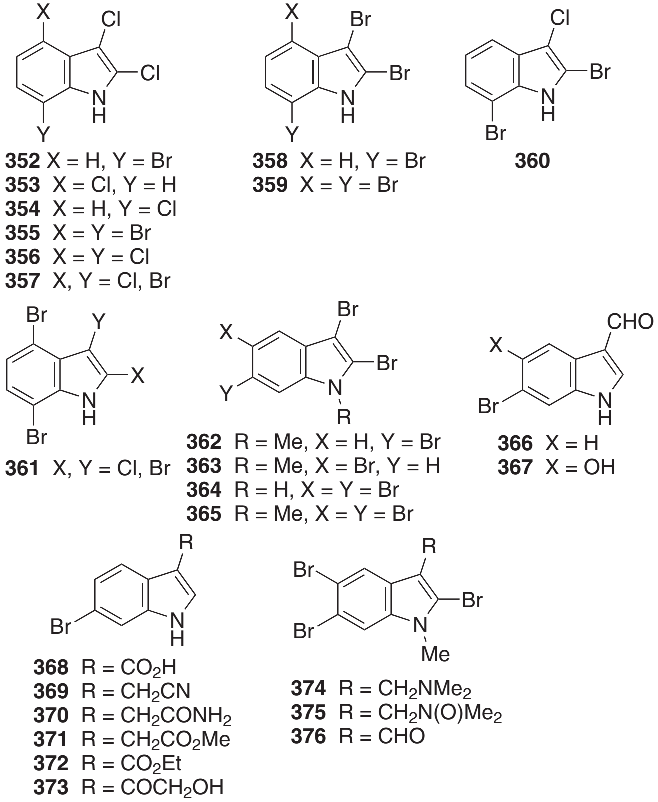

332 X = H, Y = OMe
333 X = Br, Y = H
337 X = Br, Y = OMe
334 X = Cl, Y = H
335 X = Br, Y = H
336 X = Cl, Y = Br
338 X = Y = Br
339 X = Br, Y = H
340 X = Y = H
341 X = H, Y = Me
342 X = Br, Y = Z = H
343 X = H, Y = Br, Z = H
344 X = Y = H, Z = Br
345 X = Br, Y = Z = H, R = H
346 X = H, Y = Z = Br, R = H
347 X = H, Y = Z = Br, R = Me
348
349 R = H
350 R = OH
351

Figure 51 Halogenated indole alkaloids **332**–**351**.

(**335**) as its major odorous component,[296] along with **340** and **341**.[298] 3,6-Dibromoindole (**338**) is also found in the Palauan ascidian *Distaplia regina*,[299] and 3-chloroindole (**334**) has been identified in the mushroom *Hygrophorus paupertinus*.[300] The common edible oyster *Crassostrea virginica* contains two dibromoindoles and one tribromoindole, yet to be identified.[301] In addition to 3,6- (**338**) and 4,6- (**340**) dibromoindoles, the open ocean and sediments in the North and Baltic Seas contain 4- (**342**), 5- (**343**), 6- (**344**) bromoindole, and 3,4-dibromoindole (**345**).[302] The Chinese red alga *Laurencia similis* has afforded 3,5,6-tribromoindole (**346**), the 1-methyl derivative (**347**), and 2,3,6-tribromoindole (**348**).[303] The predatory gastropod *Drupella fragum*, which preys on corals, contains 6-bromo-5-hydroxyindole (**349**), 6-bromo-4,5-dihydroxyindole (**350**), and 5-bromo-4,7-dihydroxyindole (**351**).[304] Synthesis confirmed the structure of **349**, a compound with potent antioxidant activity that is superior to α-tocopherol and comparable to BHT.

Algae are a prolific source of halogenated indole alkaloids, none more so than the New Zealand red alga *Rhodophyllis membranacea* the source of



352 X = H, Y = Br
353 X = Cl, Y = H
354 X = H, Y = Cl
355 X = Y = Br
356 X = Y = Cl
357 X, Y = Cl, Br

358 X = H, Y = Br
359 X = Y = Br

360

361 X, Y = Cl, Br

362 R = Me, X = H, Y = Br
363 R = Me, X = Br, Y = H
364 R = H, X = Y = Br
365 R = Me, X = Y = Br

366 X = H
367 X = OH

368 R = CO_2H
369 R = CH_2CN
370 R = CH_2CONH_2
371 R = CH_2CO_2Me
372 R = CO_2Et
373 R = $COCH_2OH$

374 R = CH_2NMe_2
375 R = $CH_2N(O)Me_2$
376 R = CHO

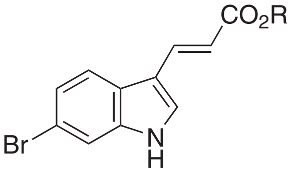
Figure 52 Halogenated indole alkaloids **352–376**.

352–361, although the exact structures of **357** and **361** are unknown, as are several additional polyhaloindoles that are present in the mass spectra of extracts[305] (Figure 52). Polybrominated indoles **362–365** are found in the Caribbean red alga *Laurencia brongniartii*.[306] The Indian Ocean *Aplysia dactylomela* sea hare also contains **363** and **365**,[307] perhaps from the algae diet of this animal, and the sponge *Oceanapia bartschi* is found to contain 3-bromoindole (**335**) and 6-bromo carbaldehydes **366** and **367**.[308] Aldehyde **366** also occurs in a marine *Pseudomonas* sp.,[309] the coral *Dendrophyllia* sp.,[310] and sponges *Pleroma menoui*,[311] *Plocamissma igzo*,[312] *Pseudosuberites hyalinus*,[313] *Halichondria* sp.,[314] ascidian *Stomozoa murrayi*, [315] and an *Acinetobacter* sp. associated with this ascidian.[315] The deep-water sponge *Pseudosuberites hyalinus* also contains 6-bromoindoles **368–371**[313] and the Coral Sea *Pleroma menoui* has furnished **372** and **373**.[311] The gramine analogs **374** and **375** are found in the bryozoan *Zoobotryon verticillatum*. Amine

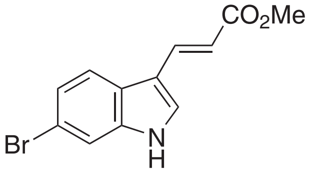
N-oxide **375** is the first marine alkaloid *N*-oxide to be discovered.[316] This organism also produces aldehyde **376**.[317]

Several 3-indoleacrylates have been isolated from sponges, such as **377** from *Iotrochota* sp.,[318] penaresin (**378**) from the Okinawan sponge *Penares* sp.,[319] **377** and **379** from the Coral Sea sponge *Corallistes undulatus*,[320] and igzamide (**380**) from *Plocamissma igzo*[312] (Figure 53).

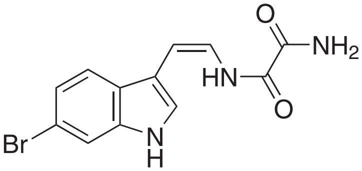
The novel sulfate-sulfamate ancorinolates A (**381**) and B (**382**) are found in the sponge *Ancorina* sp.[321] (Figure 54). The simple bromoanaindolone (**383**) was characterized in the cyanobacterium *Anabaena constricta* as an unequal mixture of enantiomers.[322]



377 R = Me
378 R = H
(penaresin)

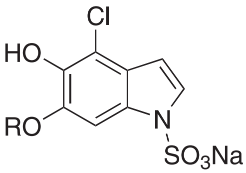


379

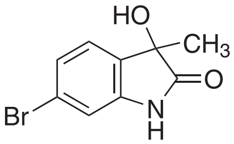


380 (igzamide)

Figure 53 Bromoindole alkaloids **377–380**.

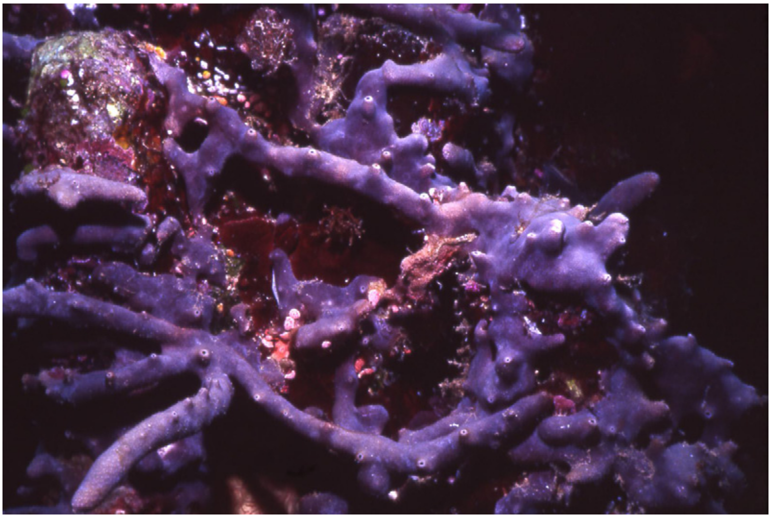


381 R = SO_3Na (ancorinolate A)
382 R = H (ancorinolate C)



383 (bromoanaindolone)

Figure 54 Halogenated indole alkaloids **381–383**.



Dysidea granulosa, a cyanobacterium-containing sponge.

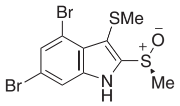
Photo 8: Professor Francis J. Schmitz.

The red seaweed *Laurencia brongniartii* is a repository of a plethora of sulfur-containing haloindoles, such as itomanindoles A (**384–385**) and B (**386**),[323] and indoles **387–393**[324,325] (Figure 55). A Formosian collection of this alga has yielded the related **394–396**.[326]

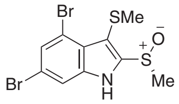
The polybrominated bis-indoles **397–399** are also present in *Laurencia brongniartii*[324,326] (Figure 56). Although the axial chiral **398** was isolated in optically active form, **397** and **399** had no optical rotation. A similar collection of polybrominated bis-indoles (**400–406**) is found in the cyanobacterium *Rivularia firma*.[327,328] Alkaloids **400–404** are also optically active due to axial chirality, [225,329] but **405** and **406** were not isolated in optically active form.

Brominated tryptamines and modified analogs comprise a very large group of halogenated alkaloids in the marine environment (Figure 57). The simple 5,6-dibromotryptamine (**407**) and it *N*-methyl derivative **408** are present in the sponge *Polyfibrospongia maynardii*,[330] **409** and **410** occur in *Smenospongia aurea*, [331,332] and **410** is present in *S*. (=*Polyfibrospongia*) *echina*.[331] An ascidian *Eudistoma fragum* contains **409**,[333] and the tunicate *Didemnum candidum* has yielded 6-bromotryptamine (**411**).[334] The sponge *Pachymatisma johnstoni* contains L-6-bromohypaphorine (**412**), [335] while epimer **413** is present in an Okinawan *Aplysia* sp. sponge.[336] The related 5-bromo analog **414** of **412** is found in the sponge *Thorectandra* sp. as is 5-bromo-*N*,*N*-dimethyltryptophan (**415**).[337]

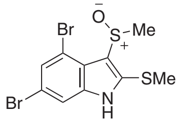
A Philippine sponge *Smenospongia* sp. contains 5-bromotryptophan (**416**), 5-bromoabrine (**417**), 5,6-dibromoabrine (**418**), and 5-bromoindol-3-yl-acetic



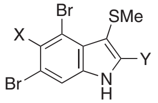
384 (itomanindole A)



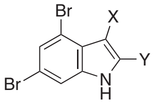
385 (itomanindole A)



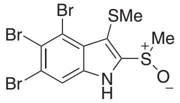
386 (itomanindole B)



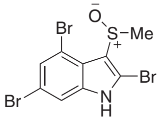
387 X = H, Y = Br
388 X = Y = Br
389 X = H, Y = SMe
390 X = Br, Y = SMe



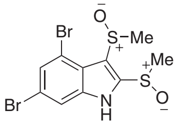
391 X = H, Y = Br
392 X = Y = Br
393 X = H, Y = SMe



394

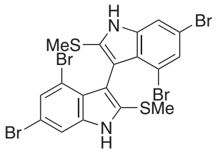


395

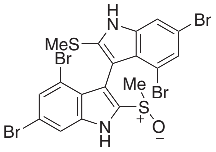


396

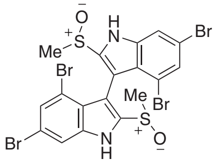
Figure 55 Sulfur-containing bromoindole alkaloids **384–396**.



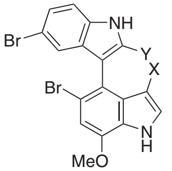
397



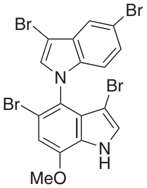
398



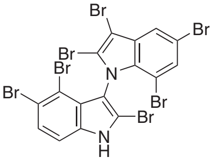
399



400 X = Y = Br
401 X = Br, Y = H
402 X = H, Y = Br

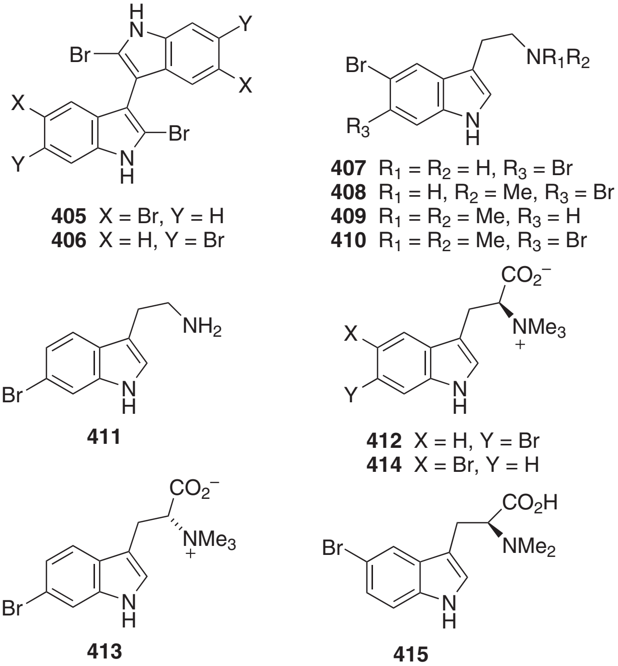


403



404

Figure 56 Brominated biindole alkaloids **397–404**.



405 X = Br, Y = H
406 X = H, Y = Br

407 $R_1 = R_2 = H, R_3 = Br$
408 $R_1 = H, R_2 = Me, R_3 = Br$
409 $R_1 = R_2 = Me, R_3 = H$
410 $R_1 = R_2 = Me, R_3 = Br$

411

412 X = H, Y = Br
414 X = Br, Y = H

413

415

Figure 57 Bromotryptamines and related alkaloids **405–415**.

acid (**419**)[338] (Figure 58). Methyl 6-bromoindole-3-carboxylate (**420**) was characterized in the Papua New Guinean sponge *Smenospongia* sp.[337] The rare iodine-containing plakohypaphorines A–F (**421–426**) are present in the Caribbean sponge *Plakortis simplex*.[339,340] Indeed, these alkaloids are the first examples of naturally occurring iodinated indoles.

The Tasmanian bryozoan *Amathia convoluta* produces convolutindole A (**427**),[341] and *Flustra foliacea*, a bryozoan from the North Sea, contains deformylflustrabromine B (**428**),[342] **429**, **430**, and deformylflustrabromine **431**[343] (Figure 59). We shall learn more about this prolific animal later.

Polyandrocarpamides A (**432**) and B (**433**) were isolated from the Philippine ascidian *Polyandrocarpa* sp.,[344] while the similar chelonin B (**434**) and bromochelonin B (**435**) were found in the Palauan sponge *Chelonaplysilla* sp.[345] (Figure 60). Disulfide citorellamine (**436**) is present in the Fijian tunicate *Polycitorella mariae*.[346,347] A snail from the Pacific coast, *Calliostoma canaticulatum*, produces disulfide **437**, which repels the predatory starfish *Pycnopodia helianthoides*.[348]

The brominated aplysinopsin analog **438** was isolated from the aforementioned *Thorectandra* sp. sponge,[337] but the first such brominated imidazolinyl-indole alkaloid found in marine life is the 6-bromoaplysinopsin

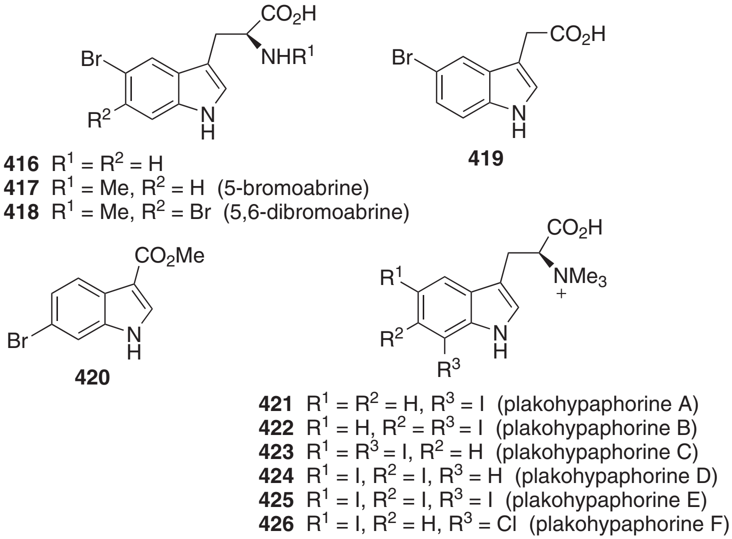


Figure 58 Halogenated indole alkaloids **416**–**426**.

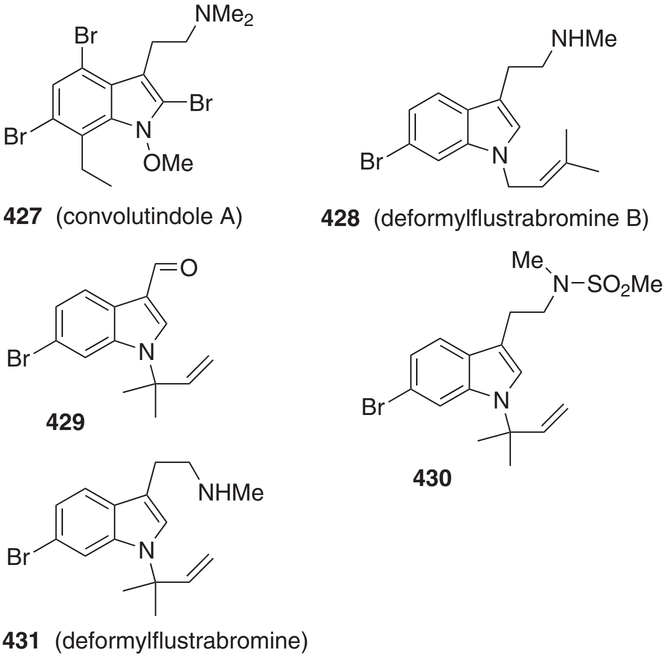


Figure 59 Bromoindole alkaloids **427**–**431**.

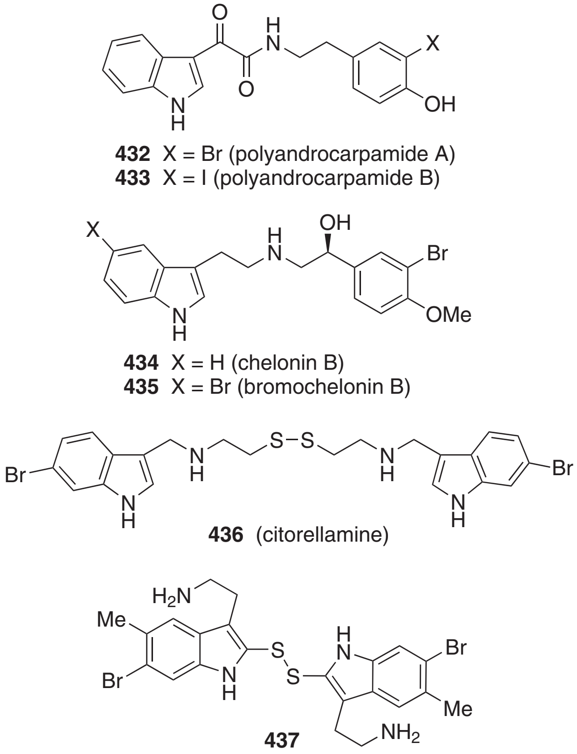
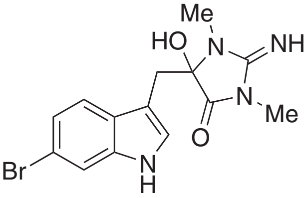


Figure 60 Bromoindole alkaloids **432**–**437**.

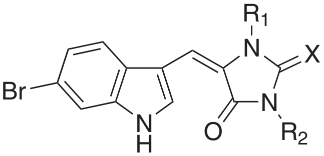
439, found in a *Dercitus* sp. sponge[349] (Figure 61). This discovery was followed by the isolation of **440** from *Smenospongia aurea*, [331] along with **441** and **442**,[332] and **441** and **443** from the Mediterranean anthozoan *Astroides calycularis*.[350]

The *E*/*Z* mixture of bromoaplysinopsins **444** and **445** is found in the coral *Tubastraea* sp., and **440** and **446** are present in the coral *Leptopsammia pruvoti*[351] (Figure 62). Similarly, the coral *Dendrophyllia* sp. contains *E*/*Z* mixtures of **439**/**447** and **448**/**449**.[310] These alkaloids undergo facile photochemical interconversion favoring the *E*-isomer and thermal reversal to an equilibrium mixture of >95:5 *Z*/*E*.[310] Note that for convenience, **439** and **442** are depicted as the exocyclic imine tautomer. The deep-water Bahamian sponge *Discodermia polydiscus* contains the cytotoxic **450**,[352] and 6-hydroxydiscodermindole (**451**),[353] both of which are optically active. The sponge *Hyrtios erecta* produces the dibromoaplysinopsins **452** and **453**.[354]

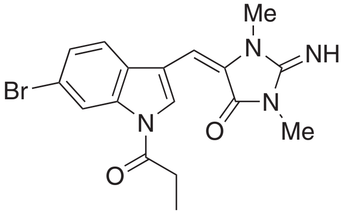
Kottamides A–E (**454**–**458**) were identified in the New Zealand ascidian *Pycnoclavella kottae*[355,356] (Figure 63). All of these alkaloids are biologically



438

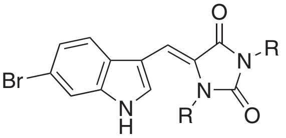


439 X = NH, R_1 = H, R_2 = Me
440 X = O, R_1 = R_2 = H
441 X = NH, R_1 = R_2 = Me
442 X = NH, R_1 = Me, R_2 = H
444 X = O, R_1 = R_2 = Me

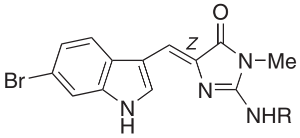


443

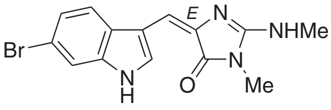
Figure 61 Brominated aplysinopsin alkaloids **438**–**444**.



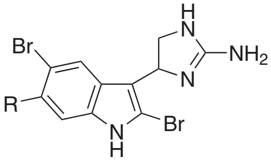
445 R = Me
446 R = H



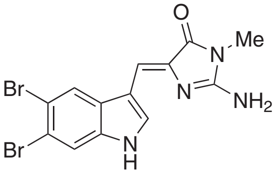
447 R = H
448 R = Me



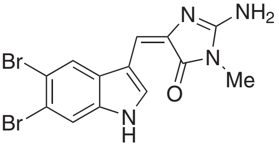
449



450 R = H
451 R = OH

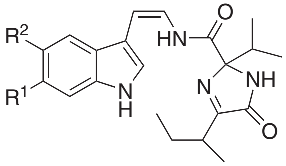


452

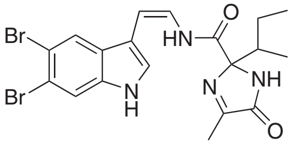


453

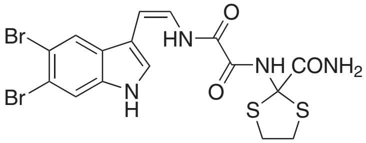
Figure 62 Brominated aplysinopsin alkaloids **445**–**453**.



454 $R^1 = R^2 = Br$ (kottamide A)
455 $R^1 = Br, R^2 = H$ (kottamide B)
456 $R^1 = H, R^2 = Br$ (kottamide C)



457 (kottamide D)



458 (kottamide E)

Figure 63 Brominated kottamide alkaloids **454–458**.

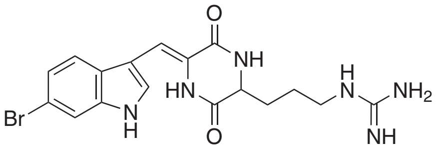
active (antiinflammatory, antitumor, antimetabolic) and kottamide E (**458**) contains the unusual 1,2-dithiolane ring. Kottamides A–D are optically active, whereas kottamide E is achiral. The relative and absolute configurations of these alkaloids are unknown.

Barettin (**459**) and dihydrobarettin (**460**) are found in the Swedish sponge *Geodia baretti*.[357–360] The absolute and relative configurations of **459** and **460** have not been reported. The three novel 6-bromoindole peptides **461–463** were isolated from the New Caledonian ascidian *Leptoclinides debius*[361] (Figure 64). Alkaloid **463** possesses the rare amino acid enduracididine.

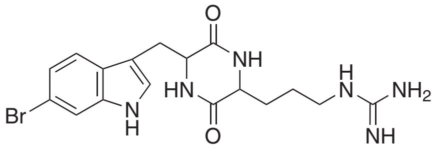
The North Carolinian coast has yielded alternatamides A–D (**464–467**) from the bryozoan *Amathia alternata*[362] (Figure 65).

Bunodosine 391 (**468**) is a toxic component of the venom of the sea anemone *Bunodosoma cangicum*,[363] and the novel ketoamide didemnidine B (**469**) was found in the New Zealand ascidian *Didemnum* sp.[364] (Figure 66). The Australian ascidian *Leptoclinides durus* was found to contain the optically active leptoclinidamine C (**470**), which features the rare 5-(methylthio)histidine unit, but whose absolute configuration is unknown.[365]

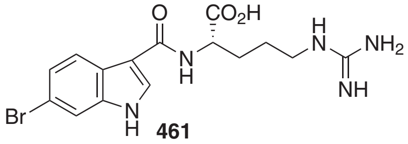
The Antarctic sponge *Psammopemma* sp. has furnished the 4-hydroxyindole alkaloids psammopemmins A–C (**471–473**) containing the unique 2-bromopyrimidine ring[366] (Figure 67). A suite of similar aminopyrimidines, meridianins



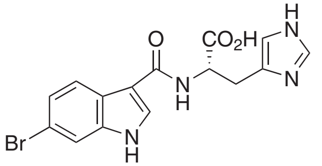
459 (barettin)



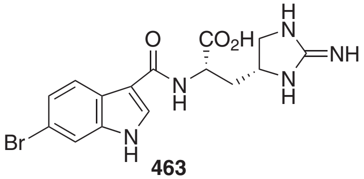
460 (8,9-dihydrobarettin)



461

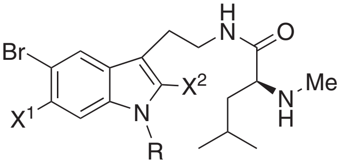


462



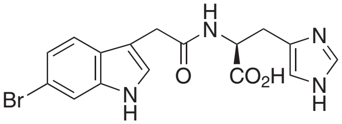
463

Figure 64 Bromoindole alkaloids **459–463**.

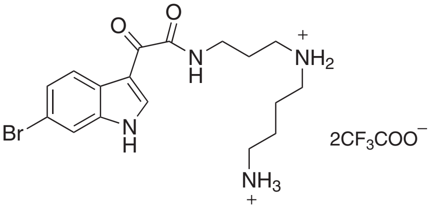


464 R = Me, $X^1 = X^2$ = Br (alternatamide A)
465 R = H, $X^1 = X^2$ = Br (alternatamide B)
466 R = X^1 = H, X^2 = Br (alternatamide C)
467 R = X^2 = H, X^1 = Br (alternatamide D)

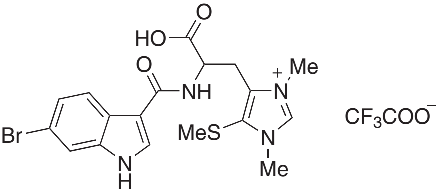
Figure 65 Brominated alternatamide alkaloids **464–467**.



468 (bunodosine 391)

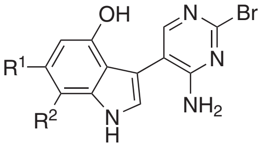


469 (didemnidine B)

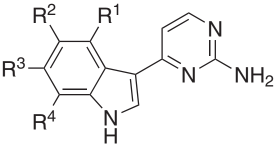


470 (leptoclinidamine C)

Figure 66 Bromoindole alkaloids **468–470**.

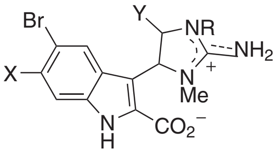


471 $R^1 = R^2 = H$ (psammopemmin A)
472 $R^1 = H$, $R^2 = Br$ (psammopemmin B)
473 $R^1 = Br$, $R^2 = H$ (psammopemmin C)

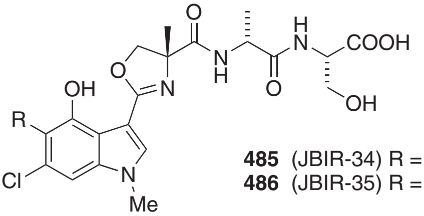


474 $R^1 = OH$, $R^2 = R^4 = H$, $R^3 = Br$ (meridianin B)
475 $R^1 = R^3 = R^4 = H$, $R^2 = Br$ (meridianin C)
476 $R^1 = R^2 = R^4 = H$, $R^3 = Br$ (meridianin D)
477 $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = Br$ (meridianin E)
478 $R^1 = R^4 = H$, $R^2 = R^3 = Br$ (meridianin F)

Figure 67 Bromoindole alkaloids **471–478**.



	X	Y	R	
479	H	H	H	(trachycladindole A)
480	H	H	Me	(trachycladindole B)
481	OH	H	H	(trachycladindole C)
482	OH	H	Me	(trachycladindole D)
483	H	OH	Me	(trachycladindole E)
484	OH	OH	Me	(trachycladindole F)



485 (JBIR-34) R = Me
486 (JBIR-35) R = H

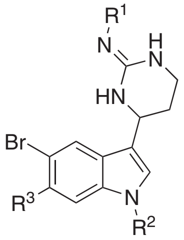
Figure 68 Brominated trachycladindoles and related alkaloids **479–486**.

B–F (**474–478**), are found in the deep water tunicate *Aplidium meridianum* from the South Georgia Islands[367–369] and also from the Antarctic tunicate *Synoicum* sp.[370] This latter study[370] has suggested that psammopemmin A (**471**) = meridianin A (debromo **474**), psammopemmin B (**472**) = meridianin E (**477**), and psammopemmin C = meridianin B (**474**) and that the structures of these psammopemmins need to be revised.

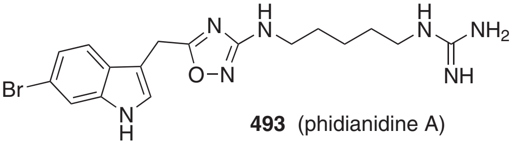
The Australian sponge *Trachycladus laevispirulifer* has yielded trachycladindoles A–F (**479–484**),[371] alkaloids similar to discodermindoles **450** and **451** (Figure 68). The relative and absolute configurations of **479–484** are unknown. A *Haliclona* sp.-derived *Streptomyces* sp. from Japan has afforded JBIR-34 (**485**) and JBIR-35 (**486**).[372]

The Antarctic tunicate *Aplidium cyaneum* has produced the optically active aplicyanins A–F (**487–492**)[373] (Figure 69). The absolute configuration of these alkaloids is unknown. The unique 1,2,4-oxadiazole-containing phidianidine A (**493**) was isolated from the mollusc *Phidiana militaris*.[374]

A large number of biologically active halogenated bis-indole alkaloids are known, particularly from sponges.[375] An early example is topsentin B2 (**494**) from the Mediterranean sponge *Topsentia genitrix*[376] and also as "bromotopsentin" from a deep-water Caribbean sponge *Spongosorites* sp. along with dihydroimidazole **495**[377] (Figure 70). A British Columbian sponge *Hexadella* sp. contains topsentin C (**496**) in addition to **494**.[378] Another deep-water sponge (460 m) *Spongosorites ruetzleri* has yielded nortopsentins A–C (**497–499**).[379]

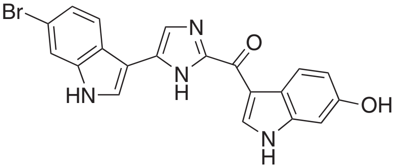


487 $R^1 = R^2 = R^3 = H$ (aplicyanin A)
488 $R^1 = Ac$, $R^2 = R^3 = H$ (aplicyanin B)
489 $R^1 = R^3 = H$, $R^2 = OMe$ (aplicyanin C)
490 $R^1 = Ac$, $R^2 = OMe$, $R^3 = H$ (aplicyanin D)
491 $R^1 = H$, $R^2 = OMe$, $R^3 = Br$ (aplicyanin E)
492 $R^1 = Ac$, $R^2 = OMe$, $R^3 = Br$ (aplicyanin F)

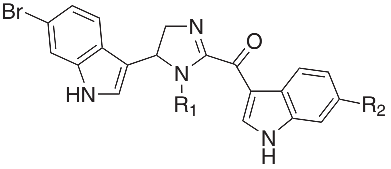


493 (phidianidine A)

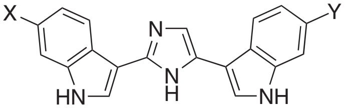
Figure 69 Brominated aplicyanin alkaloids **487**–**493**.



494 (topsentin B2)



495 $R_1 = R_2 = H$
496 $R_1 = Me$, $R_2 = Br$ (topsentin C)



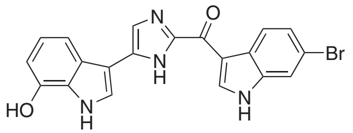
497 X = Y = Br (nortopsentin A)
498 X = Br, Y = H (nortopsentin B)
499 X = H, Y = Br (nortopsentin C)

Figure 70 Brominated topsentin alkaloids **494–499**.

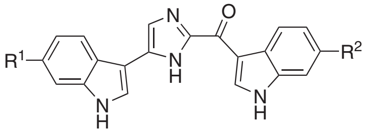
An Australian *Spongosorites* sp. contains isobromotopsentin (**500**),[380] and a Korean collection of *Spongosorites gentrix* affords bromodeoxytopsentin (**501**) and isobromodeoxytopsentin (**502**), [381] and dibromodeoxytopsentin (**503**) was found in *Spongosorites* sp.[382] (Figure 71). The related spongotines A–C (**504–506**) were also characterized from the latter sponge.[383] The Okinawan tunicate *Rhopalaea* sp. contains rhopaladins A (**507**) and C (**508**).[384]

In addition to containing the topsentin bis-indoles, many of the aforementioned sponges have yielded bis-indoles bridged by a piperazine ring. For example, dragmacidin (**509**) was found in the deep-water *Dragmacidon* sp., [385] and dragmacidons A (**510**) and B (**511**) were isolated from the British Columbian sponge *Hexadella* sp.[378] (Figure 72). The related **512** occurs in the Californian tunicate *Didemnum candidum*.[334]

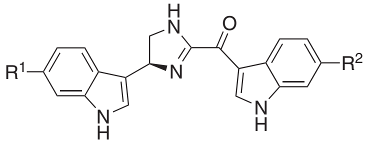
A *Spongosorites* sp. has yielded dragmacidin d (**513**)[386] (Figure 73). The deep-water sponge *Hamacantha* sp. produces the isomeric hamacanthins A (**514**) and B (**515**), inhibitors of the fungal pathogens *Candida albicans* and *Cryptococcus neoformans*.[387]



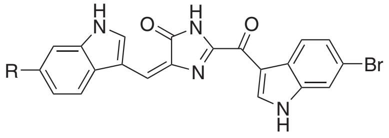
500 (isobromotopsentin)



501 R^1 = Br, R^2 = H (bromodeoxytopsentin)
502 R^1 = H, R^2 = Br (isobromodeoxytopsentin)
503 R^1 = R^2 = Br (dibromodeoxytopsentin)

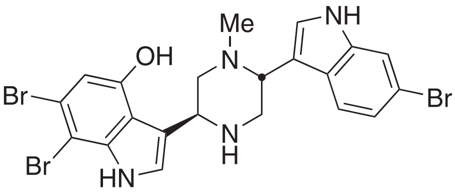


504 R^1 = Br, R^2 = H (spongotine A)
505 R^1 = H, R^2 = Br (spongotine B)
506 R^1 = R^2 = Br (spongotine C)

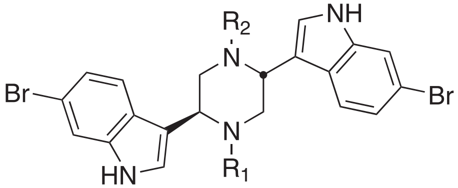


507 R = OH (rhopaladin A)
508 R = H (rhopaladin C)

Figure 71 Brominated topsentin and related alkaloids **500–508**.

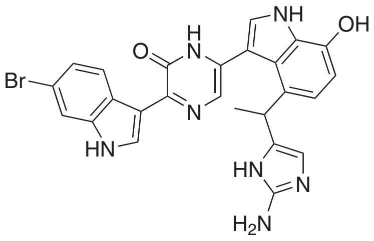


509 (dragmacidin)

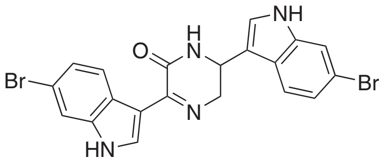


510 R_1 = H, R_2 = Me (dragmacidon A)
511 R_1 = R_2 = Me (dragmacidon B)
512 R_1 = R_2 = H

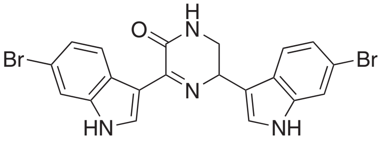
Figure 72 Brominated dragmacidin alkaloids **509–512**.



513 (dragmacidin d)

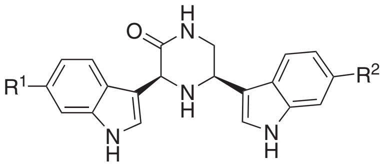


514 (hamacanthin A)

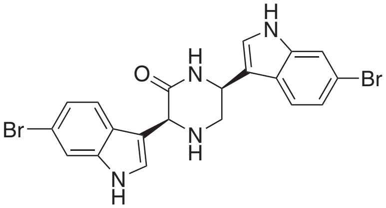


515 (hamacanthin B)

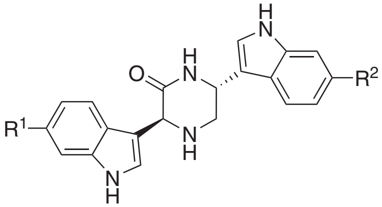
Figure 73 Bromoindole alkaloids **513–515**.



516 $R^1 = R^2 = \text{Br}$ (*cis*-3,4-dihydrohamacanthin B)
517 $R^1 = \text{H}, R^2 = \text{Br}$ (6'-debromo-*cis*-3,4-dihydrohamacanthin B)
518 $R^1 = \text{Br}, R^2 = \text{H}$ (6''-debromo-*cis*-3,4-dihydrohamacanthin B)



519 (*cis*-3,4-dihydrohamacanthin A)



520 $R^1 = R^2 = \text{Br}$ (*trans*-3,4-dihydrohamacanthin A)
521 $R^1 = \text{H}, R^2 = \text{Br}$ (6'-debromo-*trans*-3,4-dihydrohamacanthin A)
522 $R^1 = \text{Br}, R^2 = \text{H}$ (6''-debromo-*trans*-3,4-dihydrohamacanthin A)

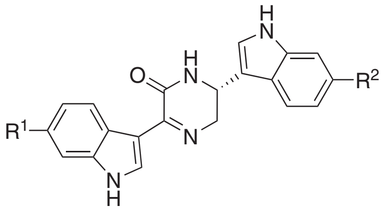
Figure 74 Brominated hamacanthin alkaloids **516**–**522**.

The Mediterranean sponge *Rhaphisia lacazei* contains seven hamacanthins **516–522** (Figure 74), and a Korean *Spongosorites* sp. has yielded **523–527**[382,383,388,389] (Figure 75).

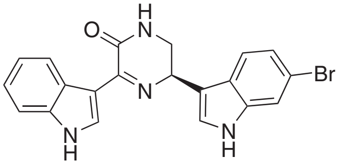
The more complex alkaloids dragmacidin E (**528**) and dragmacidin F (**529**) are found in an Australian *Spongosorites* sp.[390] and a Mediterranean *Halicortex* sp.[391] sponge, respectively (Figure 76). The Japanese stony coral *Tubastraea* sp. has produced tubastrindole A (**530**),[392] and the deep-water New Caledonian sponge *Dragmacidon* sp. contains nortopsentin D (**531**).[393]

Several novel brominated bis- and tris-tryptamines have been identified in marine organisms. In addition to the simple **532** found in the Californian tunicate *Didemnum candidum*, [334] the deep-water New Caledonian sponge (*Gellius* or *Orina* sp.) has yielded gelliusines A (**533**) and B (**534**) as racemates[394] (Figure 77).

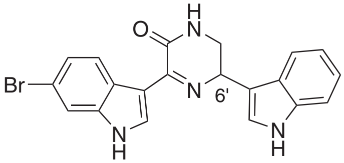
The racemic gelliusines C–F (**535–542**) were characterized from the New Caledonian sponge *Orina* sp.[395] (Figure 78).



523 R^1 = Br, R^2 = H ((*R*)-6''-debromohamacanthin A)
524 R^1 = H, R^2 = Br ((*R*)-6'-debromohamacanthin A)



525 ((*R*)-6''-debromohamacanthin B)



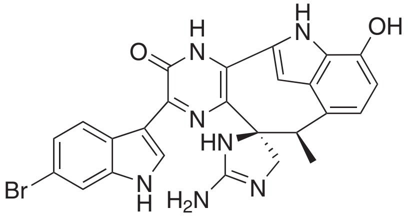
526 ((*R*)-6'-debromohamacanthin B)
527 ((*S*)-6'-debromohamacanthin B)

Figure 75 Brominated hamacanthin alkaloids **523–527**.

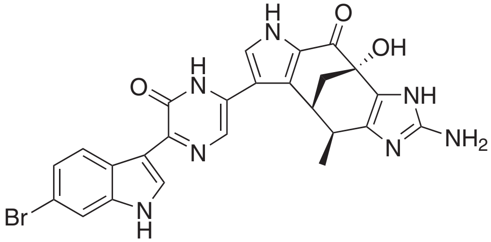
The simple 2-bromotryptamine **543** was discovered in the Mediterranean gorgonian *Paramuricea clavata* along with the isomeric **544**, which was previously synthesized but is a new natural alkaloid[396] (Figure 79). The Caribbean mangrove ascidian *Didemnum conchyliatum* produces didemnimides B (**545**) and D (**546**), and the latter is a potent feeding deterrent against local carnivorous fish.[397]

A series of related sulfur-containing bis-indoles, echinosulfonic acids B (**547**), C (**548**), and echinosulfone A (**550**), were isolated from the Australian sponge *Echinodictyum* sp.[398] (Figure 80). The related echinosulfonic acid D (**549**), along with **547**, was found in the New Caledonian sponge *Psammoclemma* sp.[399] A sponge from Papua New Guinea, *Coscinoderma* sp., has yielded coscinamides A (**551**) and B (**552**), the first alkaloids associated with this genus.[400]

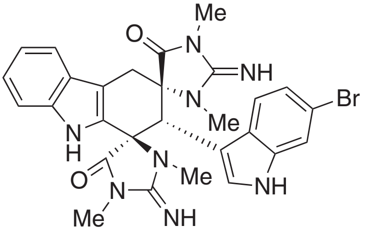
The Okinawan red alga *Laurencia brongniartii* contains five new optically inactive polybrominated bis-indoles **553–557**,[401] which are similar to **397–399** found in a Formosan collection of this same seaweed[326] (Figure 81). The interesting bromochloro bis-indole **558** occurs in the South China Sea



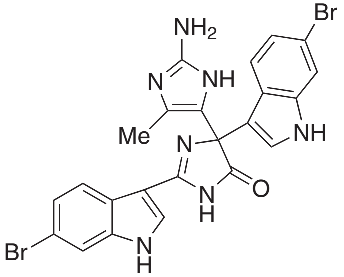
528 (dragmacidin E)



529 (dragmacidin F)



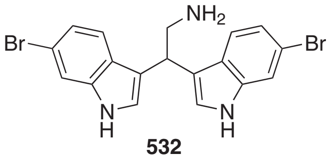
530 (tubastrindole A)



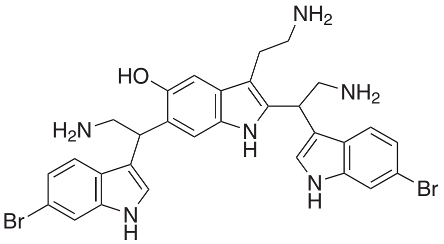
531 (nortopsentin D)

Figure 76 Bromoindole alkaloids **528**–**531**.

green alga *Chaetomorpha basiretorsa*, [402] and an Okinawan sponge *Dictyodendrilla* sp. contains optically inactive dendridine A (**559**).[403] The highly fused mixed halogenated perophoramidine (**560**) was found in the colonial ascidian *Perophora namei* from the Philippines.[404] This alkaloid is the first metabolite of any type to be identified in this genus.

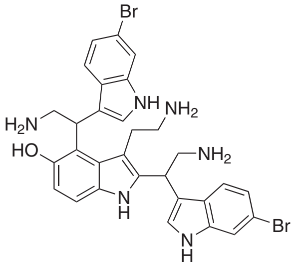


532

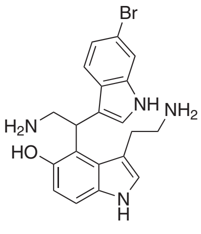


533, **534** (gelliusines A and B)

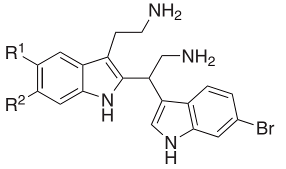
Figure 77 Brominated tryptamine alkaloids **532**–**534**.



535, **536** (gelliusine C)

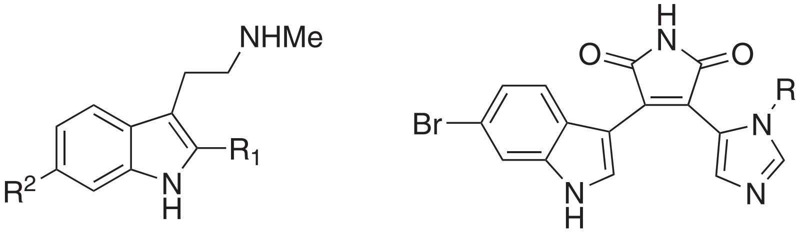


537, **538** (gelliusine C)



539, **540** R^1 = OH, R^2 = H (gelliusine E)
541, **542** R^1 = H, R^2 = Br (gelliusine F)

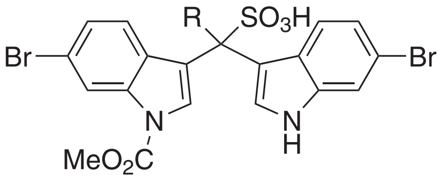
Figure 78 Brominated tryptamine alkaloids **535**–**542**.



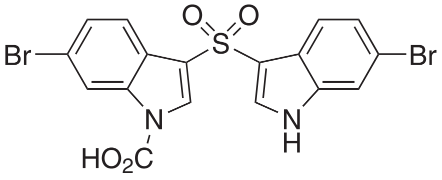
543 R^1 = Br, R^2 = H
544 R^1 = H, R^2 = Br

545 R = H (didemnimide B)
546 R = Me (didemnimide D)

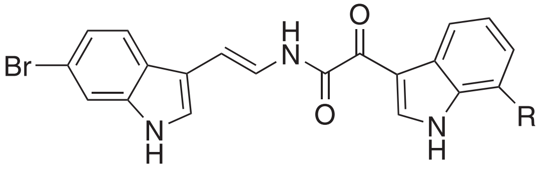
Figure 79 Bromoindole alkaloids **543–546**.



547 R = OMe (echinosulfonic acid B)
548 R = OH (echinosulfonic acid C)
549 R = H (echinosulfonic acid D)



550 (echinosulfone A)



551 R = H (coscinamide A)
552 R = OH (coscinamide C)

Figure 80 Brominated bis-indole alkaloids **547–552**.

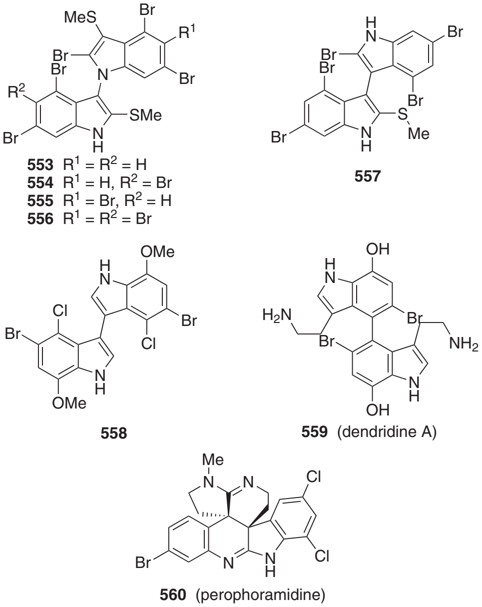
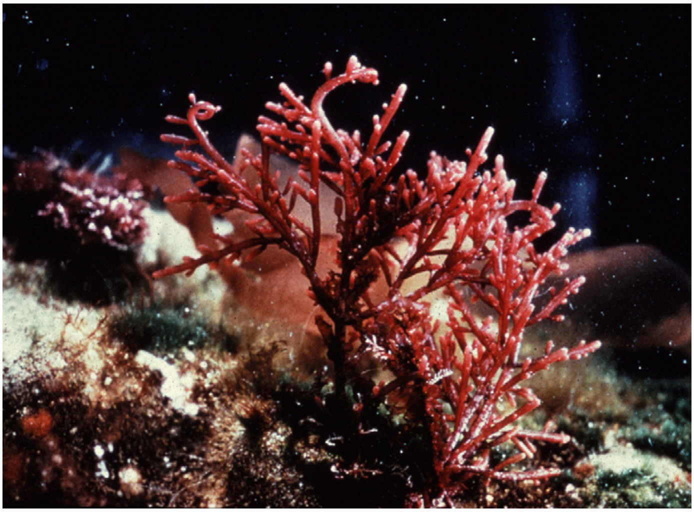


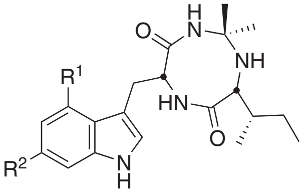
Figure 81 Brominated bis-indole alkaloids **553–560**.



Laurencia subopposita, an example of the widespread red alga genus *Laurencia*.
Photo 9: Professor William Fenical.

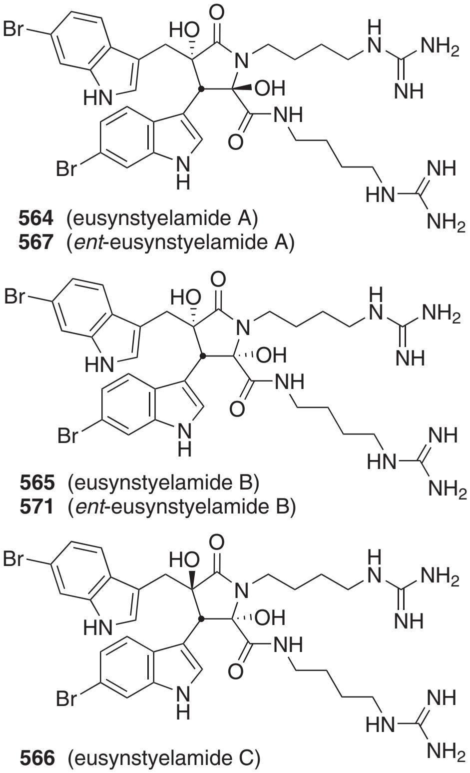
The novel iodinated hicksoanes A–C (**561**–**563**) are found in the Gulf of Aqaba gorgonian *Subergorgia hicksoni*[405] (Figure 82).

Eusynstyela latericius, an ascidian found in waters of the Great Barrier Reef, contains eusynstyelamides A–C (**564**–**566**), alkaloids possessing significant nitric oxide synthase inhibitory activity[406] (Figure 83).



561 R^1 = H, R^2 = I (hicksoane A)
562 R^1 = I, R^2 = H (hicksoane B)
563 R^1 = I, R^2 = I (hicksoane C)

Figure 82 Iodinated hicksoane alkaloids **561**–**563**.

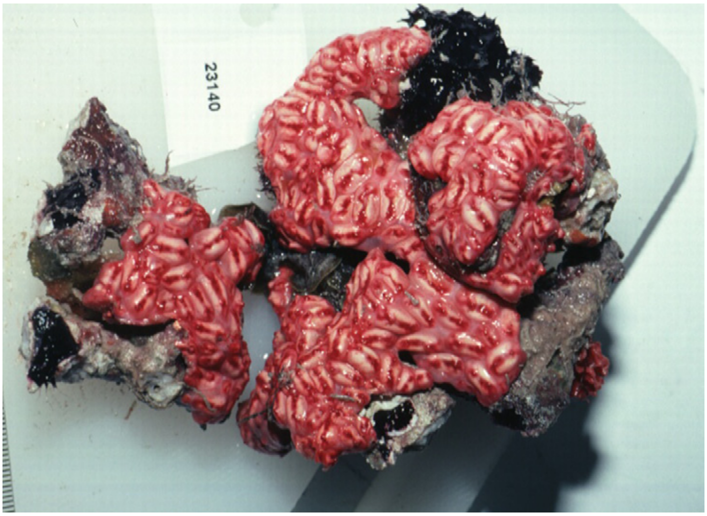


564 (eusynstyelamide A)
567 (*ent*-eusynstyelamide A)

565 (eusynstyelamide B)
571 (*ent*-eusynstyelamide B)

566 (eusynstyelamide C)

Figure 83 Brominated eusynstyelamides **564**–**567**, **571**.



Eusynstyela latericius, an ascidian found in waters of the Great Barrier Reef that contains eusynstyelamides A–C (**564–566**).

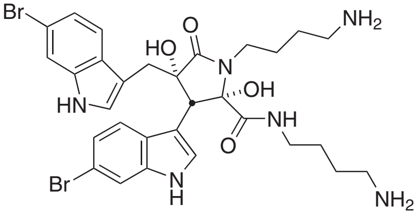
Photo 10: Dr. Carsten Wolff (supplied by Professor Anthony Wright).

An earlier report identified "eusynstyelamide" (most likely = *ent*-eusynstyelamide A (**567**), the antipode of **564**) from *Eusynstyela misakiensis*, [407] and eusynstyelamides D–F (**568–570**) along with *ent*-eusynstyelamide B (**571**), which is the antipode of **565**, have been discovered in the Arctic bryozoan *Tegella* cf. *spitzbergensis*[408] (Figure 84). The reassignment of "eusynstyelamide" (**567**) to the antipode of **564** is based on their opposite optical rotations.

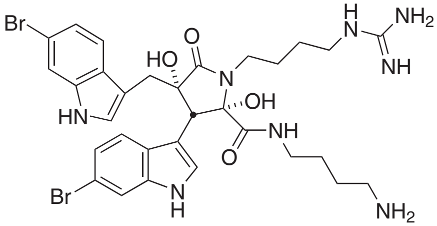
The Japanese Ivory Shell *Babylonia japonica* contains the toxins surugatoxin (**572**), neosurugatoxin (**573**), and prosurugatoxin (**574**)[409–413] (Figure 85). The latter two toxins are produced by bacteria,[413] and **572** is linked to human illness in Suruga Bay.

The novel bis-indole pyrroles, lynamicins A–E (**575–579**) were found in a marine *Marinispora* sp. actinomycete from California[414] (Figure 86). These alkaloids are active against a range of drug-resistant pathogens. Compounds **578** and **579** are related to lycogalic acid dimethyl ester.

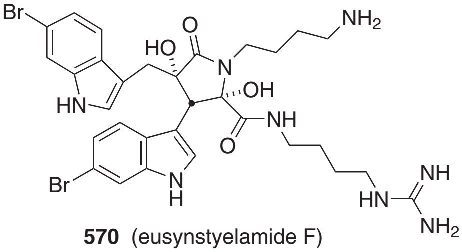
In addition to the cyanobacterial bromoanaindolone (**383**), several other halogenated oxindole alkaloids are known. The actinomycete *Nocardia blackwellii* from a Japanese soil sample produces indiscocin (**580**), which features a unique isonitrile function[415] (Figure 87). The Floridian bryozoan *Amathia convoluta* contains optically active convolutamydines A–E (**581–585**).[416–418] The absolute configuration of **581** and **582** was established by total synthesis.[419–421] Optically active matemone (**586**) was discovered in the Indian Ocean sponge *Iotrochota purpurea*, an alkaloid that inhibits



568 (eusynstyelamide D)



569 (eusynstyelamide E)

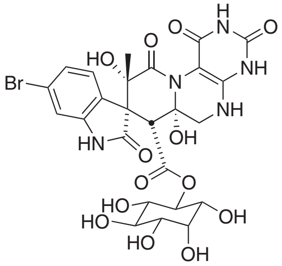


570 (eusynstyelamide F)

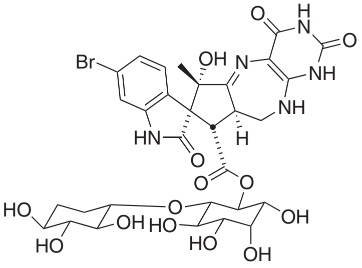
Figure 84 Brominated eusynstyelamides **568–570**.

the division of sea-urchin eggs.[422] The trichloro cynthichlorine (**587**) is found in the Moroccan tunicate *Cynthia savignyi*.[423] The optical properties of **587** were not disclosed.

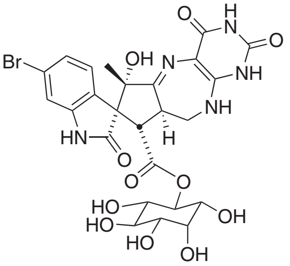
In a different territory, the terrestrial bacterium *Pseudomonas aureofaciens* produces 7-chloroindole-3-acetic acid (**588**)[424] (Figure 88). The ubiquitous plant growth hormones methyl 4-chloroindol-3-ylacetate (**589**) and 4-chloroindol-3-ylacetic acid (**590**) are present in many plants and vegetables: *Pisum sativum* (green peas),[425–427] *Vicia faba* (fava bean),[427–429] *Lathyrus latifolius* (perennial pea),[427] *Vicia amurensis* (perennial vetch),[430] *Lathyrus sativus* (grasspea),[431] *Lathyrus maritimus* (sea pea),[431] *Lathyrus odoratus* (sweet pea),[431] *Vicia sativa* (vetch),[431] *Lens culinaris* (lentil),[431] and *Pinus sylvestris* (Scots pine).[435] These metabolites are usually found in the seeds and seem to be crucial for seed development.[432–434,436] Acid **590** is 10–100 times more active as a hormone than ester **589**.[428,430,436,437] *Pisum sativum* contains (*S*)-4-chlorotryptophan (**591**)[438,439] and malonyl amides **592** and



572 (surugatoxin)

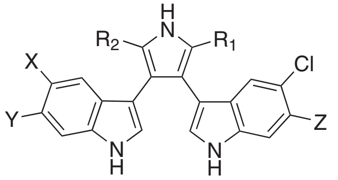


573 (neosurugatoxin)



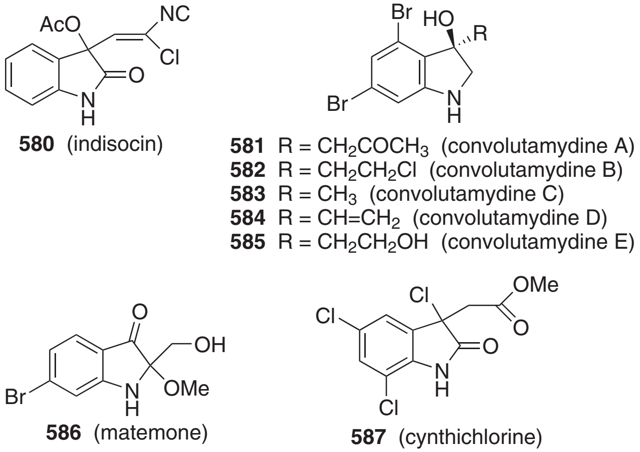
574 (prosurugatoxin)

Figure 85 Brominated surugatoxins **572**–**574**.



575 $R_1 = CO_2Me$, $R_2 = H$; X = Cl, Y = Z = H (lynamicin A)
576 $R_1 = CO_2Me$, $R_2 = H$; X = Y = Cl, Z = H (lynamicin B)
577 $R_1 = R_2 = H$; X = Y = Z = Cl (lynamicin C)
578 $R_1 = R_2 = CO_2Me$; X = Cl, Y = Z = H (lynamicin D)
579 $R_1 = R_2 = CO_2Me$; X = Y = Z = H (lynamicin E)

Figure 86 Chlorinated lynamicins **575**–**579**.



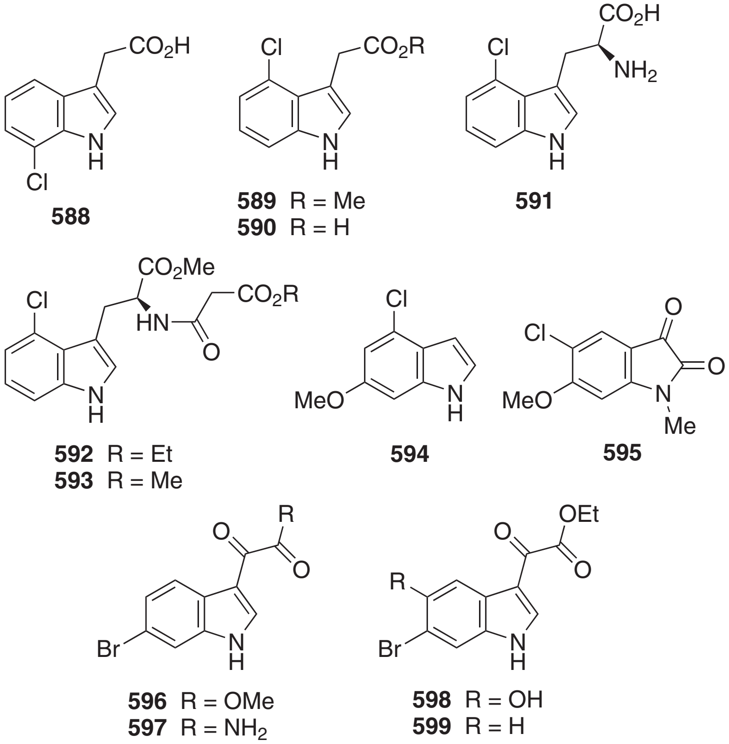
580 (indisocin)

581 R = CH_2COCH_3 (convolutamydine A)
582 R = CH_2CH_2Cl (convolutamydine B)
583 R = CH_3 (convolutamydine C)
584 R = $CH{=}CH_2$ (convolutamydine D)
585 R = CH_2CH_2OH (convolutamydine E)

586 (matemone)

587 (cynthichlorine)

Figure 87 Halogenated indoles **580–587**.



588

589 R = Me
590 R = H

591

592 R = Et
593 R = Me

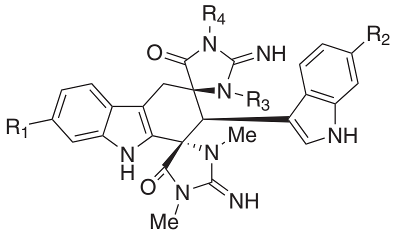
594

595

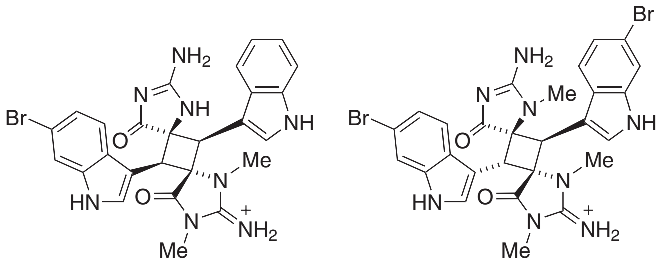
596 R = OMe
597 R = NH_2

598 R = OH
599 R = H

Figure 88 Halogenated indoles **588–599**.



600 R_1 = Br, R_2 = Br, R_3 = Me, R_4 = Me (dictazoline A)
601 R_1 = Br, R_2 = Br, R_3 = H, R_4 = H (dictazoline B)
602 R_1 = Br, R_2 = H, R_3 = H, R_4 = H (dictazoline C)
603 R_1 = Br, R_2 = H, R_3 = H, R_4 = Me (dictazoline D)



604 (dictazole A) **605** (dictazole B)

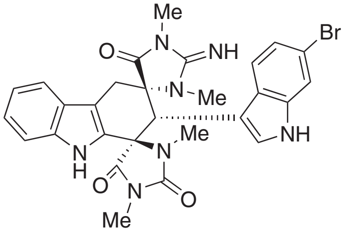
Figure 89 Brominated dictazoline and dictazole alkaloids **600–605**.

593.[439] The fava bean contains **591** and 4-chloro-6-methoxyindole (**594**).[440] This latter alkaloid may be responsible for the high incidence of stomach cancer in Columbia, via the intragastric nitrosation of **594** and subsequent carcinogenesis.[441–444] Chloroisatin **595** occurs in *Micromonospora carbonacea*.[445] The known synthetic compounds **596** and **597** have now been discovered as natural alkaloids in a Korean collection of the sponge *Spongosorites* sp.[446] Two similar alkaloids, **598** and **599**, occur in the Russian ascidian *Syncarpa oviformis*.[447]

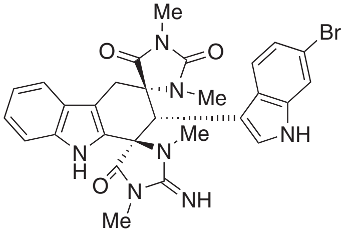
Closely related to tubastrindole A (**530**) are dictazolines A–D (**600–603**) and dictazoles A (**604**) and B (**605**), complex alkaloids produced by the Panamanian sponge *Smenospongia cerebriformis*[448,449] (Figure 89). A vinyl cyclobutane rearrangement appears to convert the dictazoles to the dictazolines. The absolute configuration of this novel alkaloid is unknown.

Related to the latter alkaloids, the new brominated tubastrindoles D (**606**) and F (**607**) were isolated from the stony coral *Tubastraea aurea*[450] (Figure 90).

The novel bromophysostigmine-pteridine alkaloids urochordamines A (**608**) and B (**609**) (epi-A) are found in the tunicate *Ciona savignyi*[451] (Figure 91).

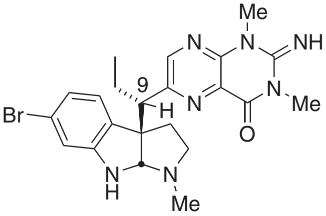


606 (tubastrindole D)



607 (tubastrindole F)

Figure 90 Brominated tubastrindoles **606–607**.

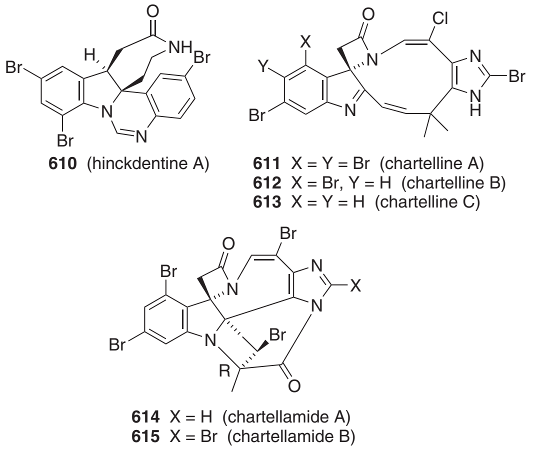


608 (urochordamine A) (C9 = *R*)
609 (urochordamine B) (C9 = *S*)

Figure 91 Brominated urochordamine alkaloids **608–609**.

The comparably complex hinckdentine A (**610**) is produced by the bryozoan *Hincksinoflustra denticulata*[452] (Figure 92). The equally unpretentious bryozoan *Chartella papyracea* has afforded the extraordinarily complex chartellines A–C (**611–613**)[453,454] and chartellamides A (**614**) and B (**615**).[455]

Competing for structural complexity with the chartellines and chartellamides are the securamines A–G (**616–622**) and cyclic tautomers securines A (**623**) and B (**624**) found in the North Sea bryozoan *Securiflustra securifrons*[456,457] (Figure 93).

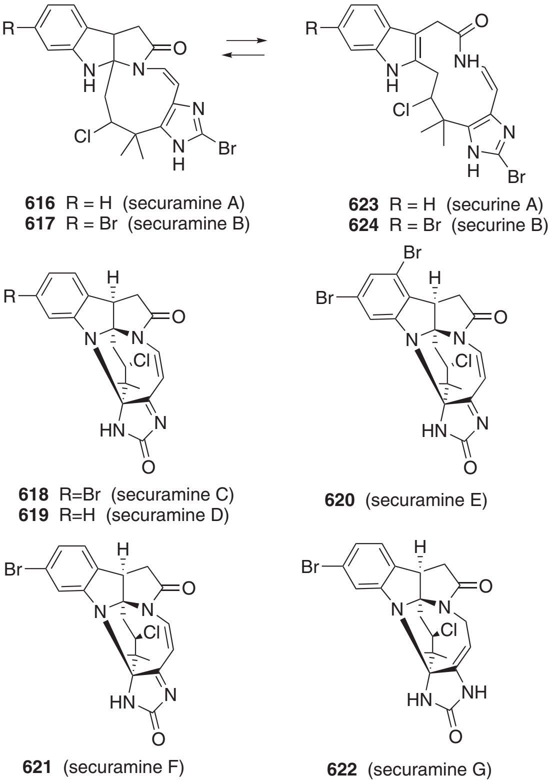


610 (hinckdentine A)

611 X = Y = Br (chartelline A)
612 X = Br, Y = H (chartelline B)
613 X = Y = H (chartelline C)

614 X = H (chartellamide A)
615 X = Br (chartellamide B)

Figure 92 Halogenated bryozoan alkaloids **610–615**.



616 R = H (securamine A)
617 R = Br (securamine B)

623 R = H (securine A)
624 R = Br (securine B)

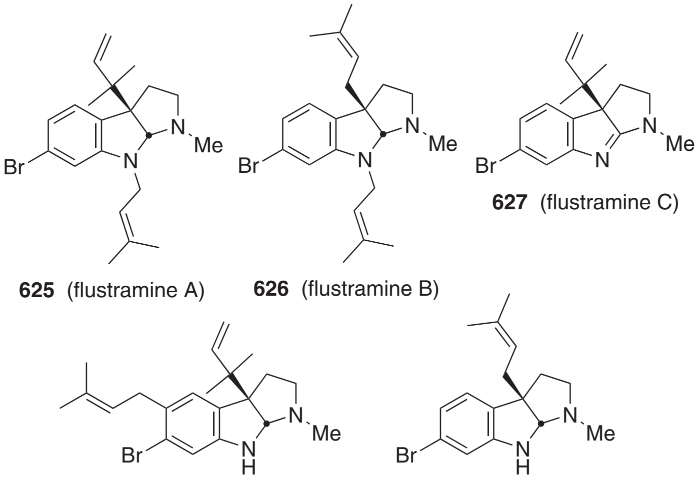
618 R=Br (securamine C)
619 R=H (securamine D)

620 (securamine E)

621 (securamine F)

622 (securamine G)

Figure 93 Halogenated securamine alkaloids **616–624**.



625 (flustramine A) **626** (flustramine B) **627** (flustramine C) **628** (flustramine D) **629** (flustramine E)

Figure 94 Brominated flustramines **625**–**629**.

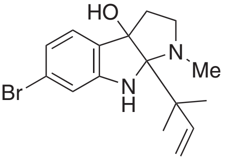
Another unobtrusive "moss," the North Sea bryozoan *Flustra foliacea*, produces an amazingly large and diverse collection of brominated physostigmine alkaloids.[458,459] Early examples include flustramines A (**625**), B (**626**),[460,461] C (**627**),[462] D (**628**),[463] E (**629**)[464] (Figure 94); flustraminols A (**630**) and B (**631**),[462] flustramides A (**632**)[465] and B (**633**)[466] (Figure 95); dihydroflustramine C (**634**)[467] and *N*-oxide **635**[463]; isoflustramine D (**636**) and flustramine D *N*-oxide (**637**)[463] (Figure 96). Flustrarine B (**638**),[466] flustrabromine (**639**),[468] formamide **640**,[465] deformylflustrabromine (**641**),[343,469] and **642** also occur in this animal.

A collection of *Flustra foliacea* from Scandinavia and Canada has yielded nine new brominated flustramine alkaloids.[470] These are flustramines F (**643**), G (**644**), H (**645**), I (**647**), J (**646**), K (**648**), L (**649**), M (**650**), and N (**651**) (Figure 97). Two dimers (not shown) may be isolation artifacts.

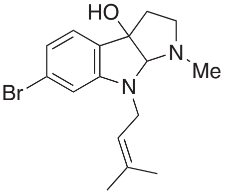
A review covering all hexahydropyrrolo[2,3-*b*]indole alkaloids, brominated and not, is available.[471]

Like bryozoa, cyanobacteria (blue–green algae) are remarkably proficient synthesizers of halogenated alkaloids. For example *Hapalosiphon fontinalis* is the source of several chlorine-containing "hapalindoles," including hapalindoles A (**652**), B (**653**), L (**654**), G (**655**), V (**656**), N (**657**), P (**658**), I (**659**), K (**660**), T (**661**), and tricyclic E (**662**) and F (**663**)[472–475] (Figure 98).

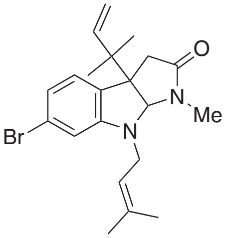
Two minor alkaloids are fontonamide (**664**) and anhydrohapaloxindole A (**665**),[475] compounds that may result from reaction of **652** with singlet oxygen (Figure 99). The blue–green alga *Fischerella* sp. has afforded hapalindolinone A (**666**),[476] and fischerindole L (**667**) occurs in the terrestrial cyanobacterium *Fischerella muscicola*.[477]



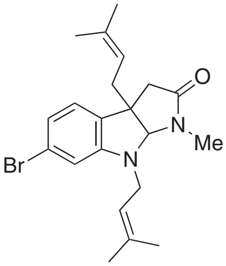
630 (flustraminol A)



631 (flustraminol B)



632 (flustramide A)



633 (flustramide B)

Figure 95 Brominated flustraminol and flustramide alkaloids **630**–**633**.

Fischerella ambigua is the source of ambiguine isonitriles A (**668**), B (**669**), D (**670**), E (**671**), and F (**672**), and hapalindole G (**655**)[478] (Figure 100). The blue–green alga *Hapalosiphon hibernicus* contains ambiguine isonitriles A (**668**) and E (**671**), while *Westiellopsis prolifica* contains D (**670**) and E (**671**).[478]

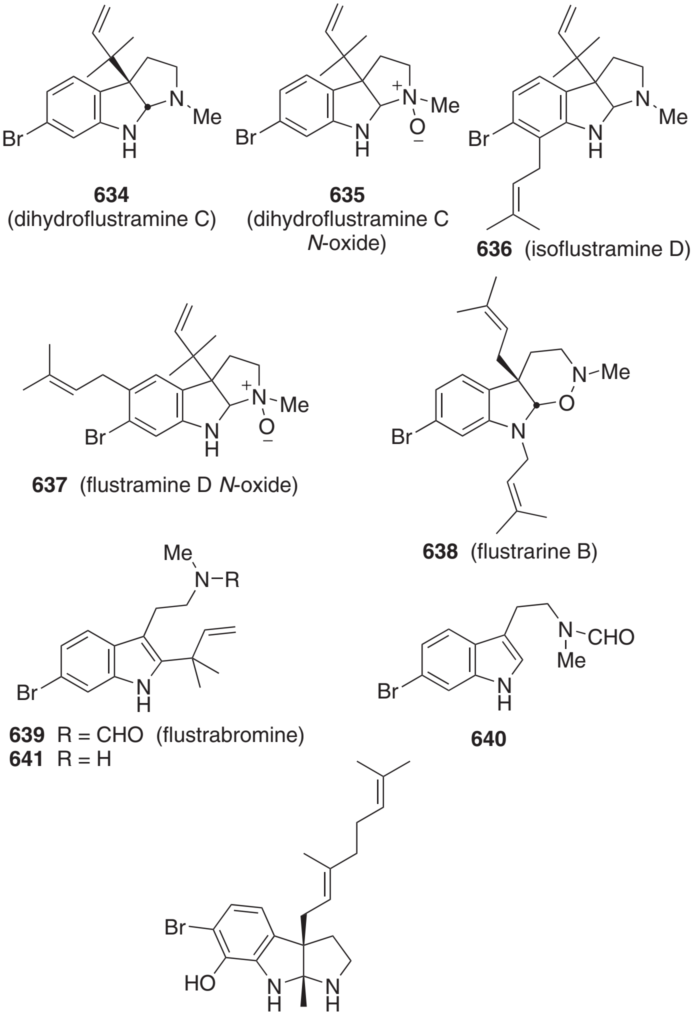
A subsequent collection of *Hapalosiphon fontinalis* yielded hapalonamide G (**673**) and V (**674**) along with anhydrohapaloxindole B (**675**)[479] (Figure 101).

The cyanobacteria *Hapalosiphon welwitschii* and *Westiella intricata* produce a plethora of chlorinated indole alkaloids related to the fischerindoles and hapalindoles.[480] The major alkaloid is *N*-methylwelwitindolinone C (**676**) accompanied by minor compounds **677**–**685** (Figure 102).

Newer examples of the hapalindoles, ambiguines, fischerindoles, and welwitindolinones continue to be characterized from cyanobacteria. *Hapalosiphon laingii* contains 12-*epi*-hapalindole G (**686**),[481] and *H. delicatulus* has yielded ambiguine G nitrile (**687**),[482] a rare marine nitrile alkaloid (Figure 103).

The terrestrial *Fischerella muscicola* produces **688** and 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**689**)[483] (Figure 104). An investigation of *Fischerella ambigua* has discovered ambiguine K (**690**), M (**691**), and O (**692**) isonitriles,[484] and fischambiguine B (**693**).[485] Both **690** and **691** show potent activity against *Mycobacterium tuberculosis* and *Bacillus anthracis*. An Israeli collection of *Fischerella* sp. is found to contain several known ambiguine isonitriles (**668**–**672**) along with new nonchlorinated analogs.[486]

The Far Eastern ascidian *Eudistoma* sp. has afforded the first marine ergoline alkaloids, pibocins A (**694**) and B (**695**)[487,488] (Figure 105). The



634
(dihydroflustramine C)

635
(dihydroflustramine C
N-oxide)

636 (isoflustramine D)

637 (flustramine D *N*-oxide)

638 (flustrarine B)

639 R = CHO (flustrabromine)
641 R = H

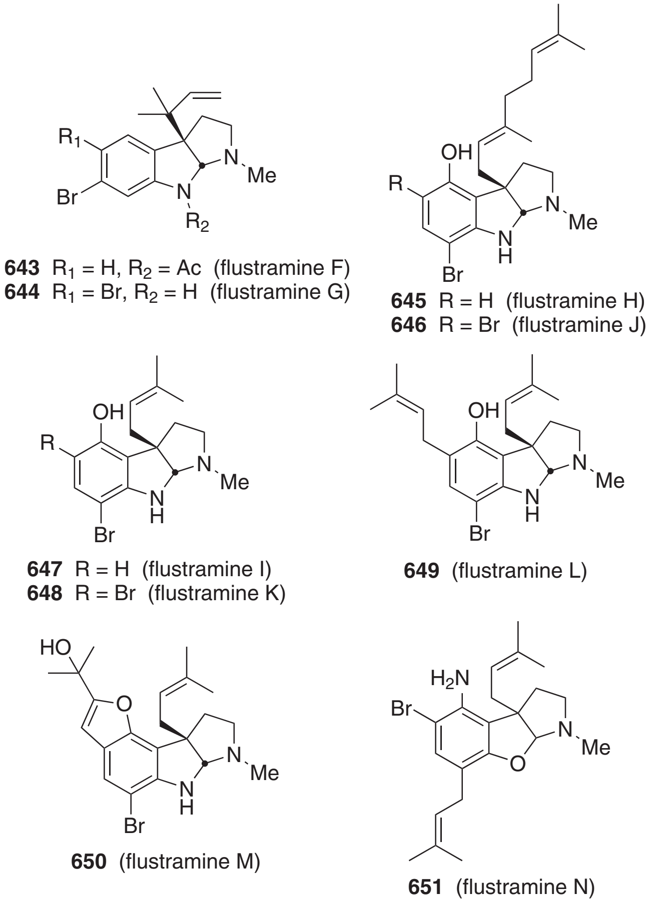
640

642

Figure 96 Brominated flustramine alkaloids **634**–**642**.

Chinese plant *Alstonia yunnanensis* contains alstoyunine H (**696**),[489] a rare halogenated monoterpenoid indole alkaloid. The possibility that **696** is an isolation artifact cannot be dismissed. The first halogenated ergot alkaloids to be identified are 8-chlororugulovasines A (**697**) and B (**698**), which are interconvertable in hot methanol.[490,491]

Streptomyces SF2582 produces pyrindamycins A (**699**) and B (**700**),[492] which were also isolated as duocarmycins C_2 (**699**) and C_1 (**700**) from *Streptomyces* DO-89[493,494] (Figure 106). These potent antitumor antibiotics



643 R_1 = H, R_2 = Ac (flustramine F)
644 R_1 = Br, R_2 = H (flustramine G)

645 R = H (flustramine H)
646 R = Br (flustramine J)

647 R = H (flustramine I)
648 R = Br (flustramine K)

649 (flustramine L)

650 (flustramine M)

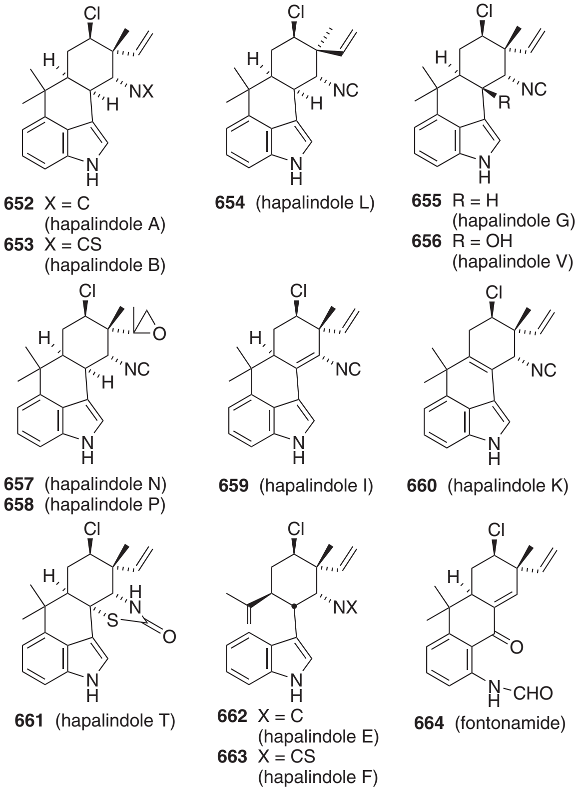
651 (flustramine N)

Figure 97 Brominated flustramine alkaloids **643–651**.

alkylate DNA via duocarmycin A.[495,496] The unnatural brominated analogs are produced by the *Streptomyces* organism when bromide is added to the culture medium. The resulting analogs are more potent than **699–700**.[496,497]

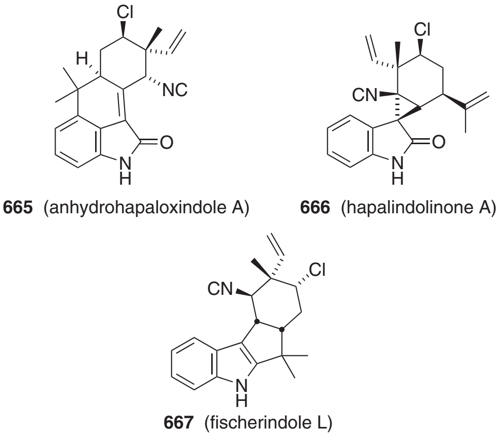
The pathogenic fungus *Sporidesmium bakeri*, which causes facial eczema in farm animals, produces sporidesmin A (**701**),[498–501] the first of a large group of sulfur-containing physostigmine-type of fungal alkaloids (Figure 107). Sporidesmin A (**701**), B (**702**), and C (**703**) occur in *Pithomyces chartarum*, another pathogenic fungus that causes eczema and liver damage in New Zealand sheep.[502–504] Subsequent research identified sporidesmins D (**704**),[505] E (**705**),[506] F (**706**),[505] G (**707**),[507,508] H (**708**),[509] and J (**709**)[509] in *P. chartarum*.

Another terrestrial fungus, *Penicillium crustosum*, is the source of an array of complex penitrems containing up to ten rings, three of which contain



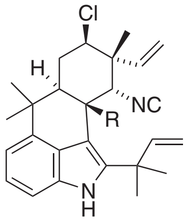
652 X = C (hapalindole A)
653 X = CS (hapalindole B)
654 (hapalindole L)
655 R = H (hapalindole G)
656 R = OH (hapalindole V)
657 (hapalindole N)
658 (hapalindole P)
659 (hapalindole I)
660 (hapalindole K)
661 (hapalindole T)
662 X = C (hapalindole E)
663 X = CS (hapalindole F)
664 (fontonamide)

Figure 98 Chlorinated hapalindole alkaloids **652**–**664**.

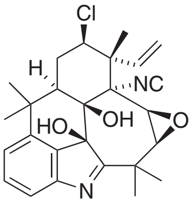


665 (anhydrohapaloxindole A)
666 (hapalindolinone A)
667 (fischerindole L)

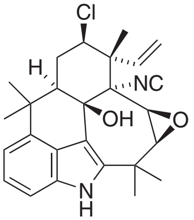
Figure 99 Chlorinated indole alkaloids **665**–**667**.



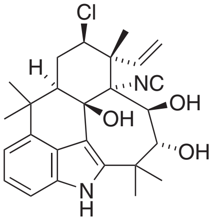
668 R = H (ambiguine isonitrile A)
669 R = OH (ambiguine isonitrile B)



670 (ambiguine isonitrile D)

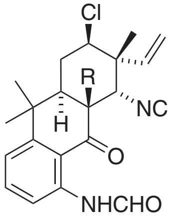


671 (ambiguine isonitrile E)

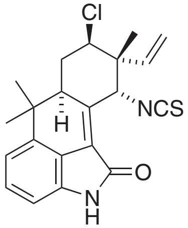


672 (ambiguine isonitrile F)

Figure 100 Chlorinated ambiguine alkaloids **668**–**672**.



673 R = H (hapalonamide G)
674 R = OH (hapalonamide V)

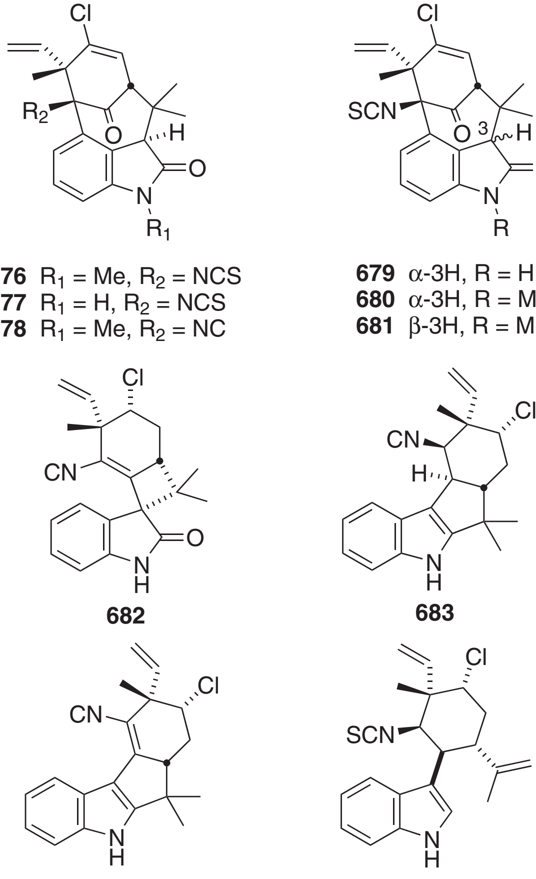


675
(anhydrohapaloxindole B)

Figure 101 Chlorinated hapalonamide alkaloids **673–675**.

chlorine: penitrems A (**710**), C (**711**), and F (**712**)[510–512] (Figure 108). Like the sporidesmins, these fungal alkaloids are highly toxic to farm animals. Pennigritrem (**713**), containing both an oxirane and oxetane ring, is produced by cultures of *Penicillium nigricans* and is a formal cyclization product of penitrem A (**710**), [513] which also occurs in *Penicillium verrucosum* var. *cyclopium*.[514] A recent cultivation of *Penicillium crustosum* has uncovered thomitrem A (**714**).[515] As a class, these indole-diterpenoids have insecticidal activity.[516]

The only known example of a halogenated pyrrolo[2,3-*b*]indole is pyrroindomycin B (**715**), which is produced by *Streptomyces rugosporus* (Figure 109). This intriguing alkaloid is active against both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*.[517] Only partial relative stereochemistry has been reported.



676 R_1 = Me, R_2 = NCS
677 R_1 = H, R_2 = NCS
678 R_1 = Me, R_2 = NC

679 α-3H, R = H
680 α-3H, R = Me
681 β-3H, R = Me

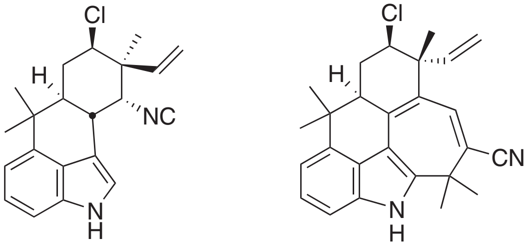
682

683

684

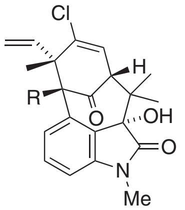
685

Figure 102 Chlorinated indole alkaloids **676**–**685**.

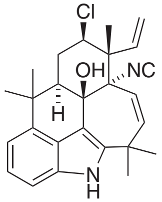


686 (12-*epi*-hapalindole G) **687** (ambiguine G nitrile)

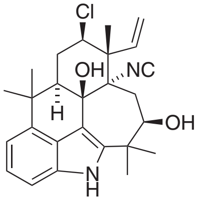
Figure 103 Chlorinated indole alkaloids **686–687**.



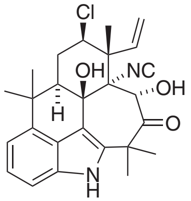
688 R = NC
689 R = NCS



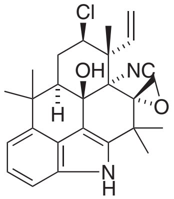
690 (ambiguine K isonitrile)



691 (ambiguine M isonitrile)

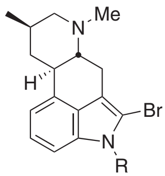


692 (ambiguine O isonitrile)

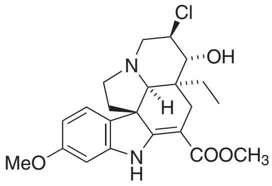


693 (fischambiguine B)

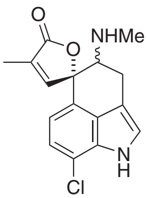
Figure 104 Chlorinated ambiguine alkaloids **688–693**.



694 R = H (pibocin A)
695 R = OMe (pibocin B)

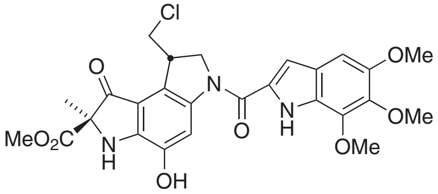


696 (alstoyunine H)

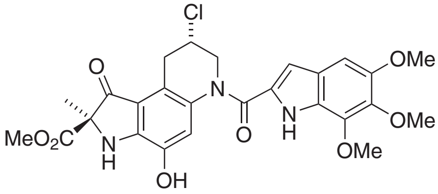


697 α-epimer (8-chlororugulovasine A)
698 β-epimer (8-chlororugulovasine B)

Figure 105 Halogenated indole alkaloids **694–698**.

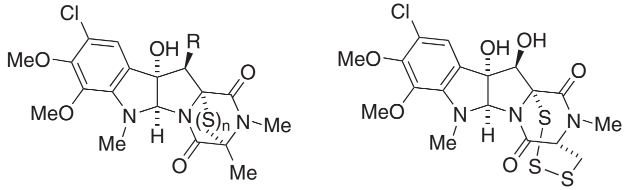


699 (pyrindamycin A = duocarmycin C$_2$)



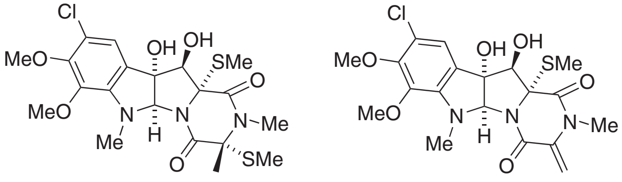
700 (pyrindamycin B = duocarmycin C$_1$)

Figure 106 Chlorinated pyrindamycin alkaloids **699–700**.



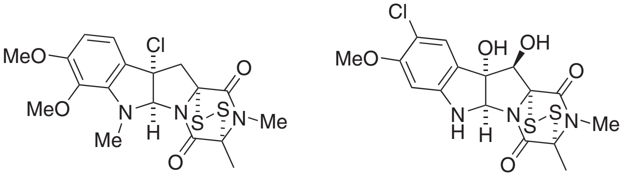
701 R = OH, n = 2 (sporidesmin A)
702 R = H, n = 2 (sporidesmin B)
705 R = OH, n = 3 (sporidesmin E)
707 R = OH, n = 4 (sporidesmin G)

703 (sporidesmin C)



704 (sporidesmin D)

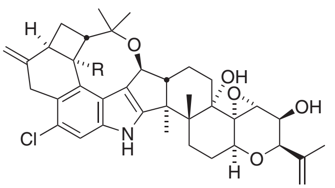
706 (sporidesmin F)



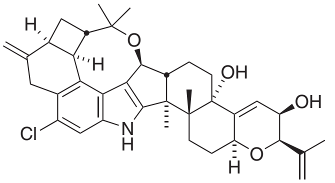
708 (sporidesmin H)

709 (sporidesmin J)

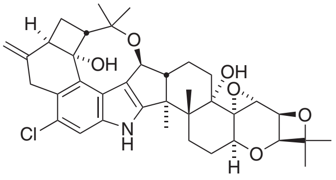
Figure 107 Chlorinated sporidesmin alkaloids **701–709**.



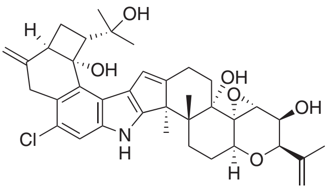
710 R = OH (penitrem A)
712 R = H (penitrem F)



711 (penitrem C)

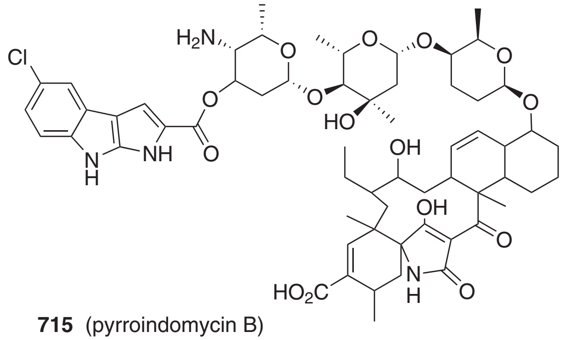


713 (pennigritrem)



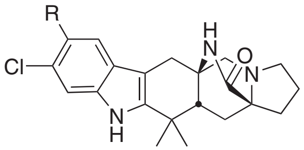
714 (thomitrem A)

Figure 108 Chlorinated penitrem alkaloids **710**–**714**.

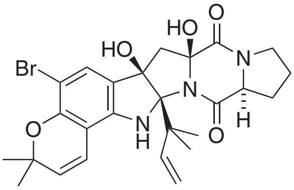


715 (pyrroindomycin B)

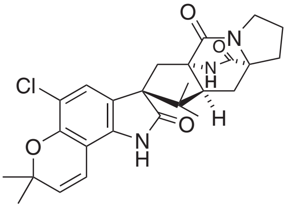
Figure 109 Chlorinated pyrroindomycin B.



716 R = Cl (malbrancheamide)
717 R = H (malbrancheamide B)



718 (notoamide P)

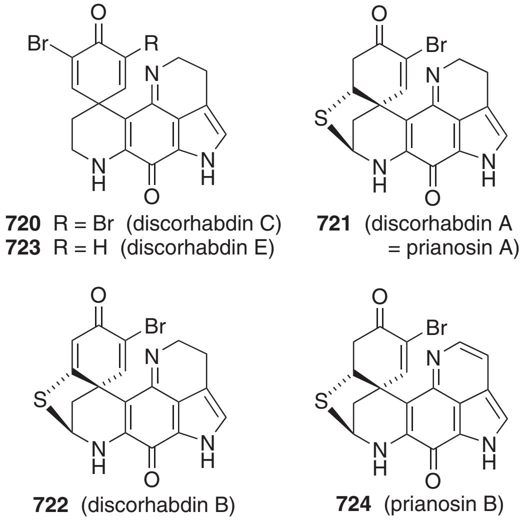


719 (notoamide N)

Figure 110 Halogenated indole alkaloids **716**–**719**.

The fungus *Malbranchea aurantiaca*, collected from bat guano in Mexico, affords malbrancheamide (**716**)[518] and malbrancheamide B (**717**)[519] (Figure 110). These novel alkaloids contain the rare bicyclo[2.2.2]diazaoctane ring system, and **716** is a unique 5,6-dichloroindole. The biosynthesis of these alkaloids has been investigated.[520] A marine-derived fungus, *Aspergillus* sp., produces the bromine-containing notoamide P (**718**), the first brominated prenylated indole alkaloid to be isolated.[521] Notoamide N (**719**) is found in a marine-derived *Aspergillus* sp. and is related to the malbrancheamides.[522]

The pyrroloiminoquinone family of modified indole alkaloids mainly embraces discorhabdins, makaluvamines, and batzellines, many of which contain bromine.[523,524] The prototype in this collection is discorhabdin C (**720**) found in the sponge *Latrunculia* sp.[525] (Figure 111). This highly cytotoxic alkaloid is the first example of a pyrrolo [1,7] phenanthroline ring system. Subsequently, discorhabdins A (**721**), B (**722**), and E (**723**) were isolated from this New Zealand sponge.[526,527] Independently, discorhabdin A (= "prianosin A") (**721**) along with prianosin B (**724**) were discovered in the Okinawan sponge *Prianos melanos*,[528,529] and **721** also occurs in the Fijian sponge *Zyzzya* cf. *marsailis*.[530]



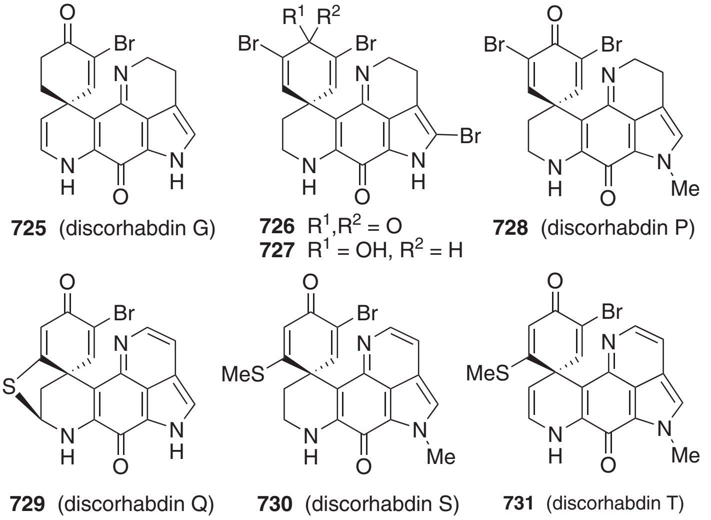
720 R = Br (discorhabdin C)
723 R = H (discorhabdin E)
721 (discorhabdin A = prianosin A)
722 (discorhabdin B)
724 (prianosin B)

Figure 111 Brominated discorhabdin alkaloids **720**–**724**.

Since these early studies, the number of identified bromine-containing discorhabdins has multiplied.[531,532] The Antarctic sponge *Latrunculia apicalis* contains discorhabdin G (**725**), a feeding deterrent toward the sea star sponge predator *Perknaster fuscus*[533,534] (Figure 112). A South African latrunculid sponge produces 14-bromodiscorhabdin C (**726**) and 14-bromodihydrodiscorhabdin C (**727**), the first such alkaloids to have a 2-bromoindole unit.[535] Discorhabdin P (**728**) occurs in the Bahamian sponge *Batzella* sp.[536] and discorhabdin Q (**729**) is found in the Australian sponges *Latrunculia purpurea*, *Zyzzya massalis*, *Z. fuliginosa*, and *Z.* spp.[537] A deep-water Caribbean sponge *Batzella* sp. has yielded discorhabdins S (**730**), T (**731**), and U (**732**).[538]

The newly described South African sponges *Tsitsikamma pedunculata*, *T. favus*, *Latrunculia bellae*, and *Strongylodesma algoensis* contain 3-dihydro-7,8-dehydrodiscorhabdin C (**733**), 14-bromo-3-dihydro-7,8-dehydrodiscorhabdin C (**734**), discorhabdin V (**735**), and 14-bromo-1-hydroxydiscorhabdin V (**736**)[539] (Figure 113). The relative stereochemistry of **735** and **736** was not assigned.

Discorhabdin W (**737**) and the 16a,17a-dehydro analog (**738**) are found in the New Zealand sponge *Latrunculia* sp.[540,541] (Figure 114). A deep-water *Latruncula* sp. sponge from Alaska has afforded dihydrodiscorhabdin B (**739**) and discorhabdin Y (**740**),[542] and the Southern Australian *Higginsia* sp. sponge contains dihydrodiscorhabdin A (**741**).[543] Unidentified deep-water green demosponges from the pre-Antarctic Indian Ocean



725 (discorhabdin G)

726 $R^1,R^2 = O$
727 $R^1 = OH, R^2 = H$

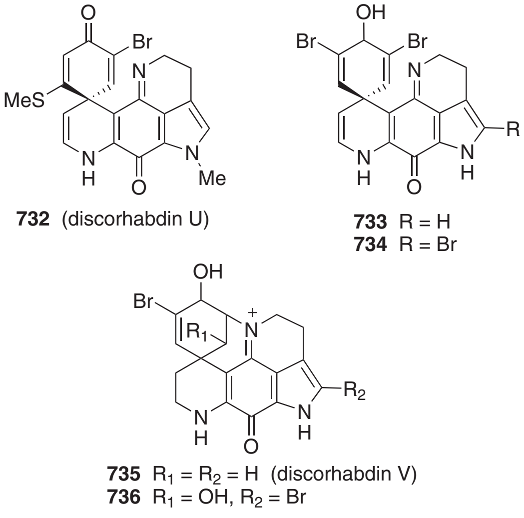
728 (discorhabdin P)

729 (discorhabdin Q)

730 (discorhabdin S)

731 (discorhabdin T)

Figure 112 Brominated discorhabdin alkaloids **725**–**731**.



732 (discorhabdin U)

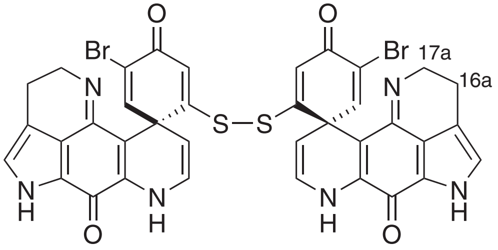
733 R = H
734 R = Br

735 $R_1 = R_2 = H$ (discorhabdin V)
736 $R_1 = OH, R_2 = Br$

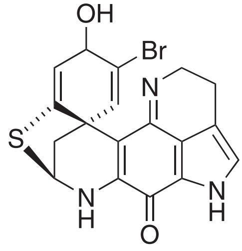
Figure 113 Brominated discorhabdin alkaloids **732**–**736**.

contain epinardins B–D (**742**–**744**),[544] obviously of the discorhabdin class. The relative configuration of **742**–**744** is known but not the absolute configuration.

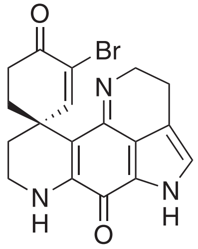
The first alkaloids of the makaluvamine-batzelline type to be isolated were makaluvamine F (**745**) and makaluvone (**746**) from the Fijian sponge



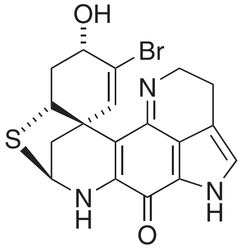
737 (discorhabdin W)
738 (16a,17a-dehydrodiscorhabdin W)



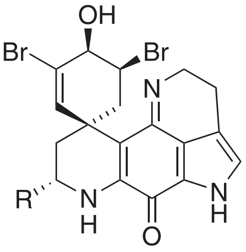
739 (dihydrodiscorhabdin B)



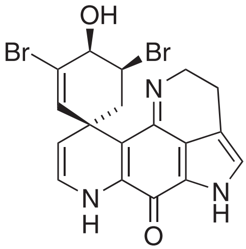
740 (discorhabdin Y)



741 (dihydrodiscorhabdin A)



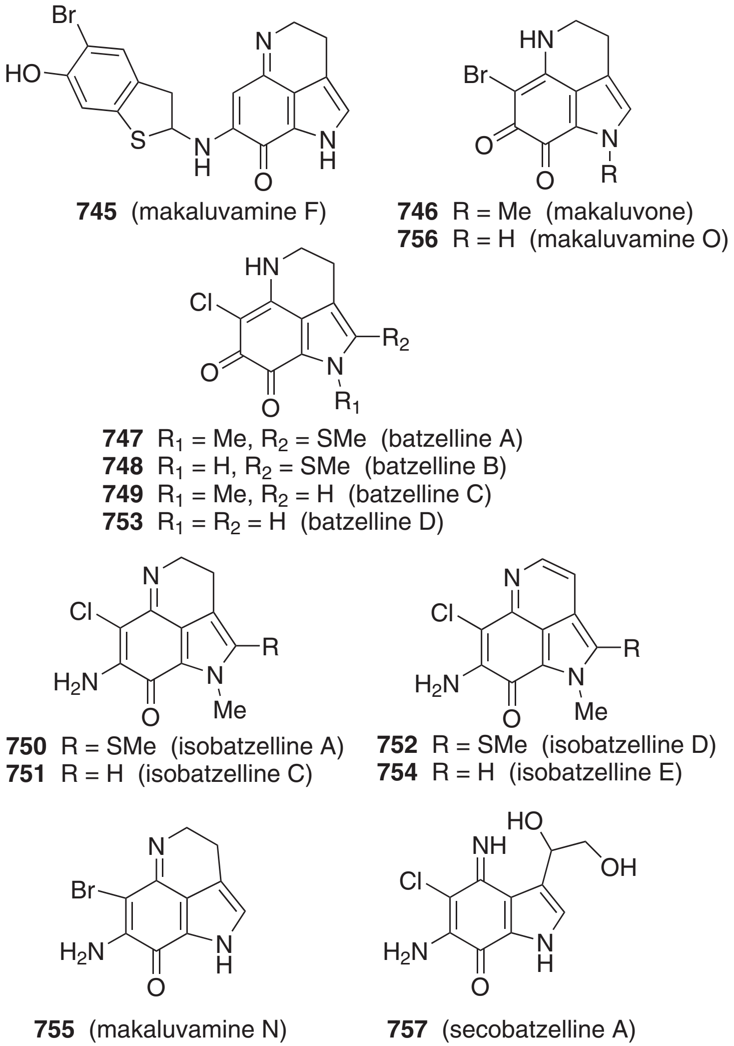
742 R = H (epinardin B)
743 R = OMe (epinardin D)



744 (epinardin C)

Figure 114 Brominated discorhabdin alkaloids **737**–**744**.

Zyzzya cf. *marsailis*[530] (Figure 115). The deep-water Bahamian sponge *Batzella* sp. produces several chlorine-containing pyrroloquinones: batzellines A (**747**), B (**748**), C (**749**),[545] and isobatzellines A (**750**), C (**751**), and D (**752**).[546] *Zyzzya fuliginosa* from Papua New Guinea contains batzelline D (**753**) and isobatzelline E (**754**),[547] while a Philippino version of this sponge has afforded makaluvamine N (**755**).[548] The Jamaican sponge *Smenospongia aurea* contains makaluvamine O (**756**),[549] and a deep-water *Batzella* sponge from the Bahamas contains secobatzelline A (**757**).[550]


745 (makaluvamine F)

746 R = Me (makaluvone)
756 R = H (makaluvamine O)

747 R_1 = Me, R_2 = SMe (batzelline A)
748 R_1 = H, R_2 = SMe (batzelline B)
749 R_1 = Me, R_2 = H (batzelline C)
753 R_1 = R_2 = H (batzelline D)

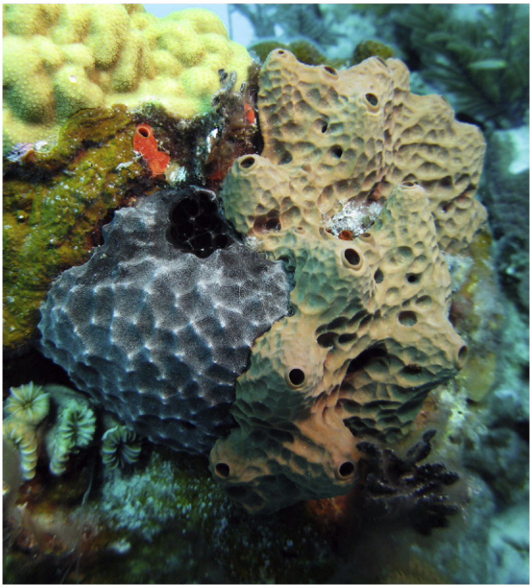
750 R = SMe (isobatzelline A)
751 R = H (isobatzelline C)

752 R = SMe (isobatzelline D)
754 R = H (isobatzelline E)

755 (makaluvamine N)

757 (secobatzelline A)

Figure 115 Halogenated makaluvamine and batzelline alkaloids **745**–**757**.



Smenospongia aurea **A marine sponge that produces the makaluvamine O 756.**

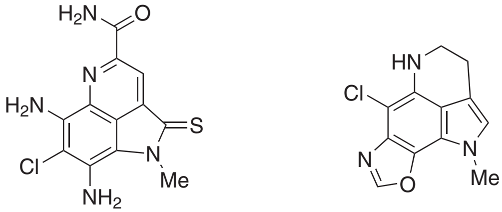
Photo 11: Professor Joseph R. Pawlik.

A marine *Streptomyces* sp. from a sediment in the Bahamas has afforded ammosamides A (**758**) and B (**759**)[551,552] (Figure 116). A new batzelline analog, citharoxazole (**760**), was found in the Mediterranean deep-water sponge *Latrunculia citharistae*.[553]

A fungus from a Chinese salt field, *Aspergillus variecolor*, produces variecolorins A (**761**), B (**762**), and F (**763**) along with several nonchlorinated analogs[554] (Figure 117).

D. Carbazoles

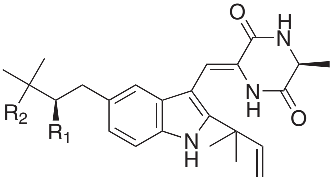
Unlike pyrroles and indoles, carbazoles are much less reactive toward electrophilic halogenation, and, as a result, far fewer halogenated carbazoles exist in nature. A notable exception is chlorohyellazole (**764**) produced by the blue–green alga *Hyella caespitosa*[555] (Figure 118). Bovine urine is the source of 3-chlorocarbazole (**765**), the first carbazole of any type to be isolated from mammals.[556,557] This compound displays potent monoamine oxidase inhibitory activity. The three dihalogenated carbazoles **766–768** were found in the encrusting cyanobacterium *Kyrtuthrix maculans* living on exposed rocky shores in Hong Kong.[558] The Brazilian ascidian *Didemnum granulatum* contains 6-bromogranulatimide (**769**),[559] a compound that is not unrelated to the indolocarbazoles to be seen later. Examination of deep



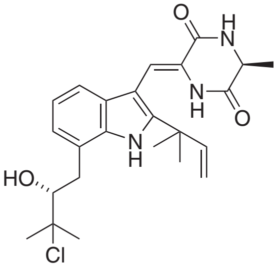
758 X = S (ammosamide A)
759 X = O (ammosamide B)

760 (citharoxazole)

Figure 116 Chlorinated indole alkaloids **758–760**.



761 R_1 = OH, R_2 = Cl (variecolorin A)
762 R_1 = Cl, R_2 = OH (variecolorin B)



763 (variecolorin F)

Figure 117 Chlorinated variecolorin alkaloids **761–763**.

sediments from Lake Michigan has uncovered several polybrominated carbazoles, including 1,3,6,8-tetrabromocarbazole (**770**), three tribromocarbazoles, another tetrabromocarbazole, and a pentabromocarbazole.[560] At one site, the highest concentration of **770**, the major congener, occurred at a core level corresponding to the year 1920, and some sediment layers dating to 1900 and earlier contained these brominated carbazoles.

E. Indolocarbazoles

A small, yet biologically significant, collection of alkaloids are the indolo [2,3-*a*]carbazoles,[561] a few of which contain halogen. The prototype of the latter is rebeccamycin (**771**) isolated from the Panamanian soil microbe *Nocar-*

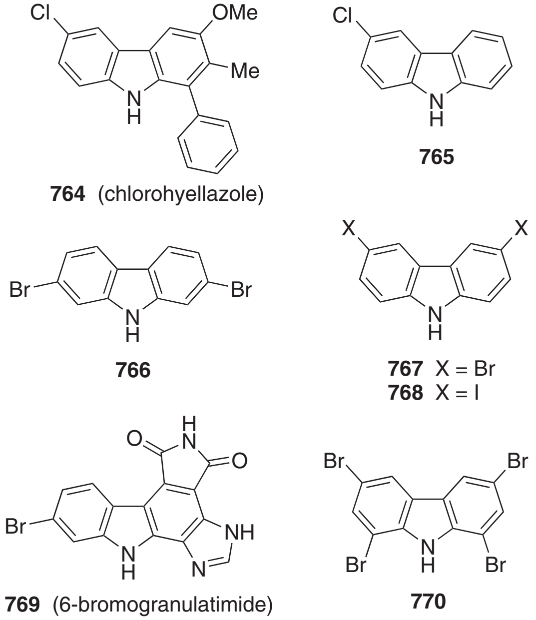


Figure 118 Halogenated carbazole alkaloids **764**–**770**.

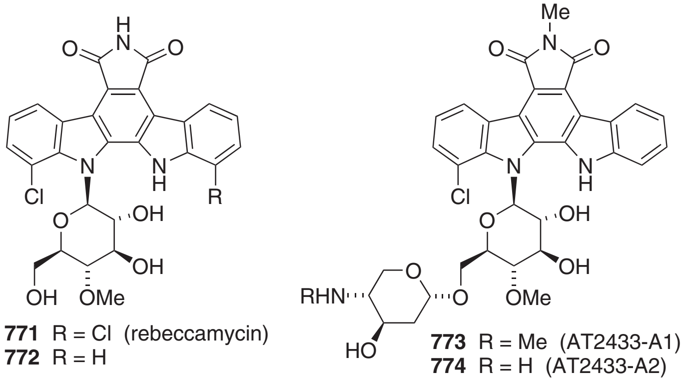
dia aerocolonigenes (renamed *Saccharothrix aerocolonigenes*)[562–564] (Figure 119). 4′-Deschlororebeccamycin (**772**) is also produced by this organism.[565] Both alkaloids exhibit pronounced antibiotic and antitumor activities.[563] In the presence of 0.05% bromide, the microbe produces the corresponding bromorebeccamycin.[566] The microbe *Actinomadura melliaura* has furnished AT2433-A1 (**773**) and -A2 (**774**), which also show pronounced biological activity.[567,568]

The blue–green alga *Tolypothrix tjipanasensis* produces an astonishing array of indolo[2,3-*a*]carbazoles, 13 of which contain chlorine: tjipanazoles A1 (**775**), A2 (**776**), C1 (**777**), C2 (**778**), C3 (**779**), C4 (**780**), B (**781**), E (**782**), F1 (**783**), F2 (**784**), D (**785**), I (**786**), and J (**787**), the absolute configurations of which are known[569] (Figure 120).

Cultures of *Streptomyces uncialis* have yielded the chlorinated cladoniamides A, B, D–G (**788–793**), which may be derived from indolocarbazole precursors[570] (Figure 121).

F. Carbolines

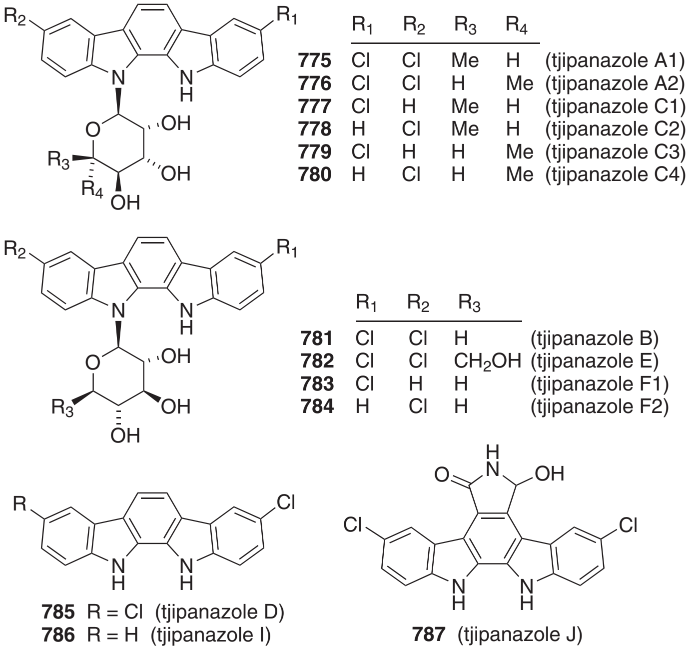
Long recognized as terrestrial plant alkaloids, β-carbolines have emerged as also comprising a large group of marine natural products, especially from ascidians (tunicates).[571] Given their presumed parentage from tryptophan, it is not surprising that many of these marine β-carbolines contain halogen.



771 R = Cl (rebeccamycin)
772 R = H

773 R = Me (AT2433-A1)
774 R = H (AT2433-A2)

Figure 119 Chlorinated indolocarbazole alkaloids **771**–**774**.



	R_1	R_2	R_3	R_4	
775	Cl	Cl	Me	H	(tjipanazole A1)
776	Cl	Cl	H	Me	(tjipanazole A2)
777	Cl	H	Me	H	(tjipanazole C1)
778	H	Cl	Me	H	(tjipanazole C2)
779	Cl	H	H	Me	(tjipanazole C3)
780	H	Cl	H	Me	(tjipanazole C4)

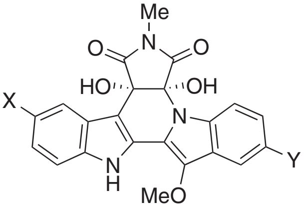
	R_1	R_2	R_3	
781	Cl	Cl	H	(tjipanazole B)
782	Cl	Cl	CH_2OH	(tjipanazole E)
783	Cl	H	H	(tjipanazole F1)
784	H	Cl	H	(tjipanazole F2)

785 R = Cl (tjipanazole D)
786 R = H (tjipanazole I)

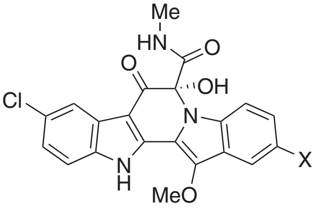
787 (tjipanazole J)

Figure 120 Chlorinated tjipanazole alkaloids **775**–**787**.

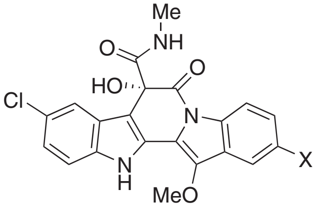
The Caribbean tunicate *Eudistoma olivaceum* typifies the prolific nature of this genus, and produces eudistomins A (**794**), C (**795**), D (**796**), E (**797**), F (**798**), G (**799**), H (**800**), J (**801**), K (**802**), L (**803**), N (**804**), O (**805**), and P (**806**)[572] (Figures 122 and 123). Another study of this tunicate from Bermuda revealed eudistomins R (**807**) and S (**808**).[573] These compounds have



788 X = Cl, Y = H (cladoniamide A)
789 X = Y = Cl (cladoniamide B)

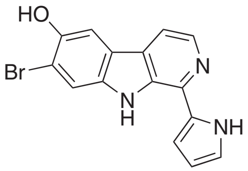


790 X = H (cladoniamide D)
791 X = Cl (cladoniamide E)

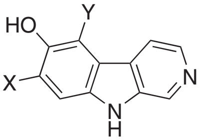


792 X = H (cladoniamide F)
793 X = Cl (cladoniamide G)

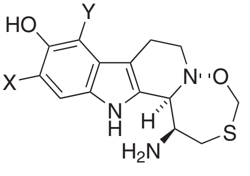
Figure 121 Chlorinated cladoniamide alkaloids **788**–**793**.



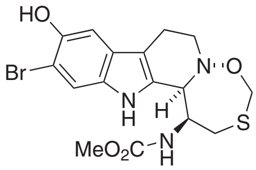
794 (eudistomin A)



796 X = H, Y = Br (eudistomin D)
801 X = Br, Y = H (eudistomin J)



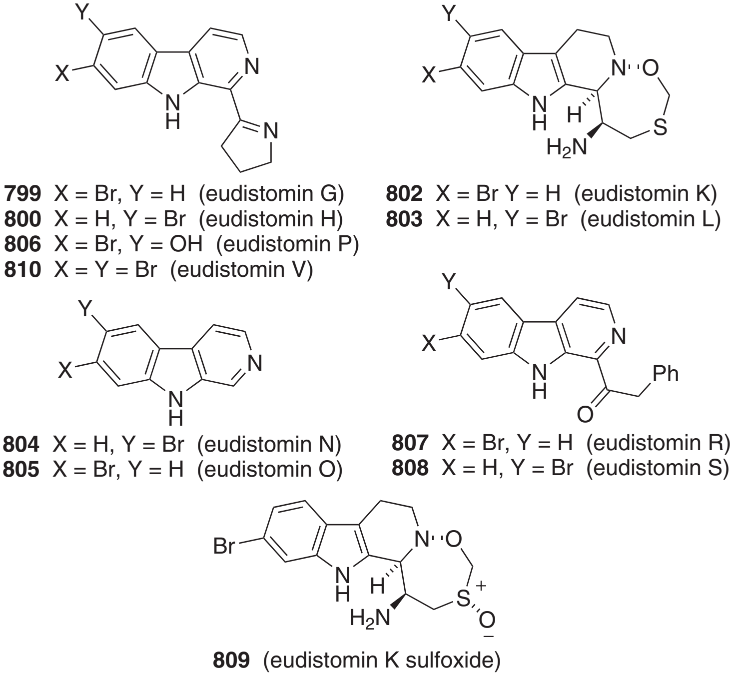
795 X = Br, Y = H (eudistomin C)
797 X = H, Y = Br (eudistomin E)



798 (eudistomin F)

Figure 122 Brominated eudistomin alkaloids **794**–**798**, **801**.

antiviral, antimicrobial, and other activities.[572] The New Zealand ascidian *Ritterella sigillinoides* has afforded eudistomin K sulfoxide (**809**), along with eudistomins K, C, and O.[574,575] The stereochemistry of the preferred invertomer of eudistomin K has been revised.[576,577] This sulfoxide displays antiviral activity against *Polio* and *Herpes*.[574] Eudistomin V (**810**) has been discovered in the Australian ascidian *Pseudodistoma aureum*.[578]



799 X = Br, Y = H (eudistomin G)
800 X = H, Y = Br (eudistomin H)
806 X = Br, Y = OH (eudistomin P)
810 X = Y = Br (eudistomin V)

802 X = Br Y = H (eudistomin K)
803 X = H, Y = Br (eudistomin L)

804 X = H, Y = Br (eudistomin N)
805 X = Br, Y = H (eudistomin O)

807 X = Br, Y = H (eudistomin R)
808 X = H, Y = Br (eudistomin S)

809 (eudistomin K sulfoxide)

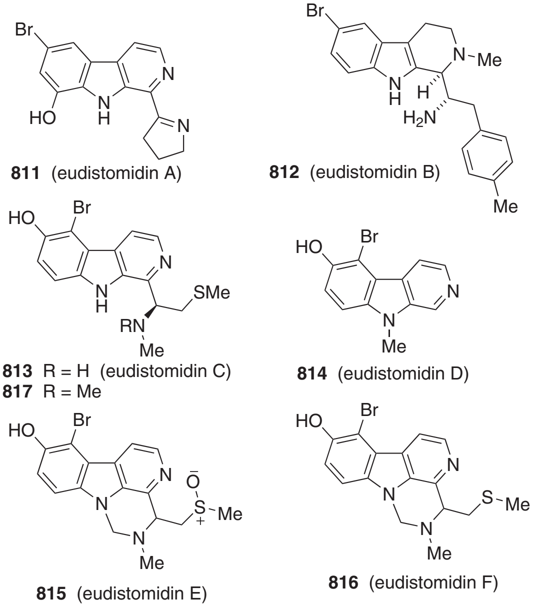
Figure 123 Brominated eudistomin alkaloids **799–810**.

Like its genus relative *Eudistoma olivaceum*, the Okinawan tunicate *Eudistoma glaucus* contains a wealth of novel brominated β-carbolines, the eudistomidins A (**811**),[579] B (**812**), C (**813**), D (**814**),[580] E (**815**), and F (**816**)[581] (Figure 124). There is evidence via synthesis that the structure of eudistomidin B (**812**) needs to be revised.[595]

The Palauan *Eudistoma gilboverde* has provided 14-methyleudistomidin C (**817**), 2-methyleudistomin D (**818**), and 2-methyleudistomin J (**819**)[582] (Figure 125). *Eudistoma album* contains eudistalbins A (**820**) and B (**821**) in addition to eudistomin E (**797**).[583]

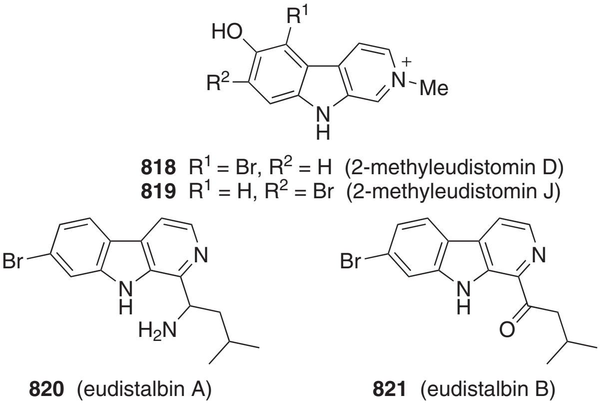
Woodinine (**822**) (relative configuration) is present in *Eudistoma fragum* from New Caledonia,[333] and the marine hydroid *Aglaophenia pluma* contains the β-carbolines **823–825**[584] (Figure 126). The terrestrial blue–green alga *Dichothrix baueriana* collected from Kauai produces bauerines A–C (**826–828**).[585]

The Okinawan *Eudistoma glaucus* continues to display its synthetic prowess with the generation of eudistomidin G (**829**)[586] (Figure 127). An undescribed Western Australia *Eudistoma* sponge contains 19-bromoisoeudistomin U (**830**).[587] A Mariana Islands ascidian *Didemnum* sp. has afforded didemnolines A (**831**) and C (**832**).[588]



811 (eudistomidin A)
812 (eudistomidin B)
813 R = H (eudistomidin C)
817 R = Me
814 (eudistomidin D)
815 (eudistomidin E)
816 (eudistomidin F)

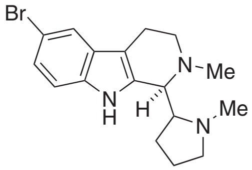
Figure 124 Bromiated eudistomidin alkaloids **811–817**.



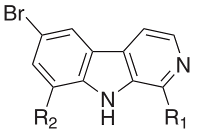
818 R^1 = Br, R^2 = H (2-methyleudistomin D)
819 R^1 = H, R^2 = Br (2-methyleudistomin J)
820 (eudistalbin A)
821 (eudistalbin B)

Figure 125 Brominated eudistomin and eudistalbin alkaloids **818–821**.

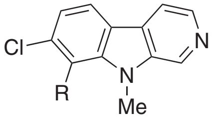
The deep-water Palauan sponge *Plakortis nigra* contains plakortamines A–D (**833–836**)[589] (Figure 128). The tunicate *Pseudodistoma arborescens* from New Caledonia has afforded arborescidines A–D (**837–840**).[590] Arborescidine A (**837**) is the brominated analog of a terrestrial indolo [2,3-*a*]quinolizine plant alkaloid. The absolute configurations of **837–840** have been tentatively assigned as shown based on the Cotton effect.



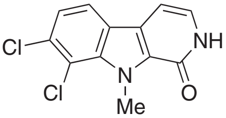
822 (woodinine)



823 R_1 = Et, R_2 = H
824 R_1 = Me, R_2 = H
825 R_1 = Et, R_2 = Br

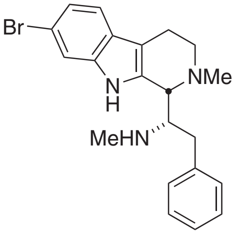


826 R = H (bauerine A)
827 R = Cl (bauerine B)

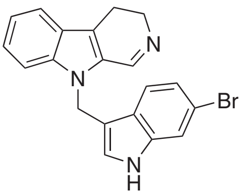


828 (bauerine C)

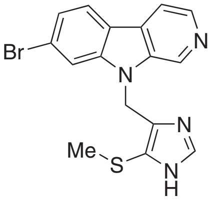
Figure 126 Halogenated carboline alkaloids **822**–**828**.



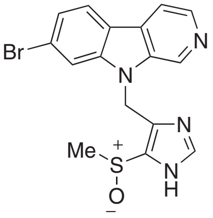
829 (eudistomidin G)



830 (19-bromoisoeudistomin U)



831 (didemnoline A)

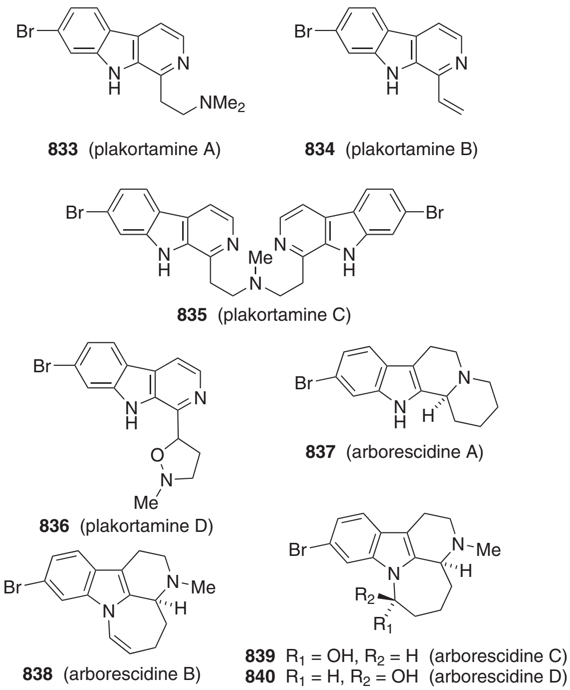


832 (didemnoline C)

Figure 127 Brominated carboline alkaloids **829**–**832**.

An Australian *Ancorina* sp. sponge contains (+)-7-bromotrypargine (**841**),[591] and the homolog (−)-7-bromohomotrypargine (**842**) is present in the New Zealand ascidian *Pseudodistoma opacum*, along with opacalines A–C (**843–845**)[592] (Figure 129). The absolute configuration of **842** is *S* as shown.

A *Eudistoma* sp. sponge from Korean waters contains eudistomins Y_2–Y_7 (**846–851**),[593] and *Eudistoma glaucus* from Okinawa has provided the new alkaloids eudistomidins H–K (**852–855**)[594] (Figure 130).



833 (plakortamine A)

834 (plakortamine B)

835 (plakortamine C)

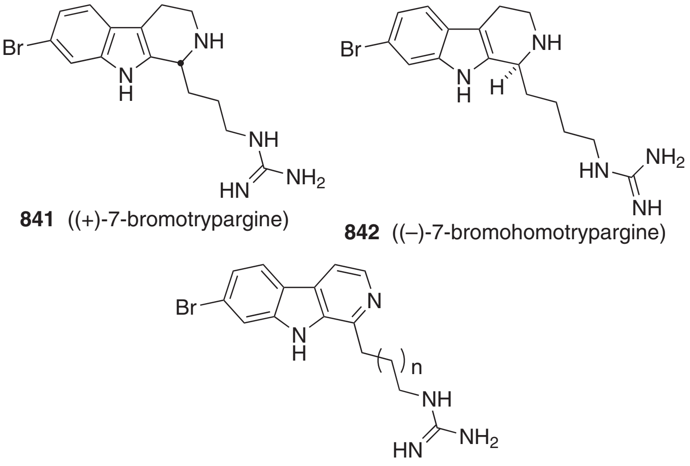
836 (plakortamine D)

837 (arborescidine A)

838 (arborescidine B)

839 R_1 = OH, R_2 = H (arborescidine C)
840 R_1 = H, R_2 = OH (arborescidine D)

Figure 128 Brominated carboline alkaloids **833**–**840**.

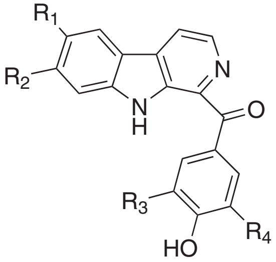


841 ((+)-7-bromotrypargine)

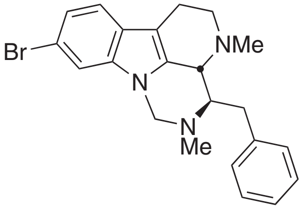
842 ((–)-7-bromohomotrypargine)

843 R = H, n = 2 (opacaline A)
844 R = OH, n = 2 (opacaline B)
845 R = H, n = 1 (opacaline C)

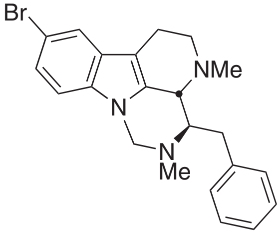
Figure 129 Brominated carboline alkaloids **841**–**845**.



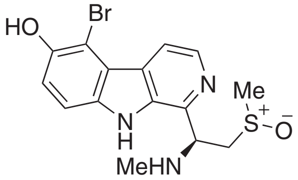
846 R_1 = Br, R_2 = H, R_3 = H, R_4 = H (eudistomin Y_2)
847 R_1 = H, R_2 = H, R_3 = Br, R_4 = H (eudistomin Y_3)
848 R_1 = Br, R_2 = H, R_3 = Br, R_4 = H (eudistomin Y_4)
849 R_1 = H, R_2 = H, R_3 = Br, R_4 = Br (eudistomin Y_5)
850 R_1 = Br, R_2 = H, R_3 = Br, R_4 = Br (eudistomin Y_6)
851 R_1 = H, R_2 = Br, R_3 = Br, R_4 = Br (eudistomin Y_7)



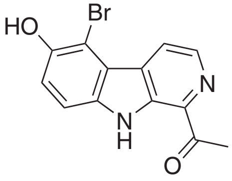
852 (eudistomidin H)



853 (eudistomidin I)



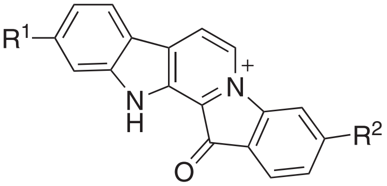
854 (eudistomidin J)



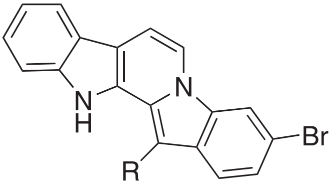
855 (eudistomidin K)

Figure 130 Brominated eudistomin alkaloids **846–855**.

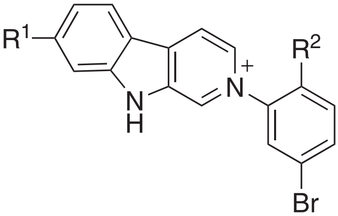
Both, the sponge *Fascaplysinopsis reticulata* and the tunicate *Didemnum* sp., yield brominated analogs of the previously known non-brominated alkaloids, fascaplysin and reticulatine. These include 3-bromofascaplysin (**856**), 14-bromoreticulatine (**857**), and 14-bromoreticulatate (**858**)[596] (Figure 131). Further examination of these organisms revealed 10-bromofascaplysin (**859**), 3,10-dibromofascaplysin (**860**), 3-bromohomofascaplysin B (**861**), 3-bromohomofascaplysin B-1 (**862**), 3-bromohomofascaplysin C (**863**), 7,14-dibromoreticulatine (**864**), 14-bromoreticulatol (**865**), 3-bromosecofascaplysin A (**866**), and 3-bromosecofascaplysin B (**867**).[597]



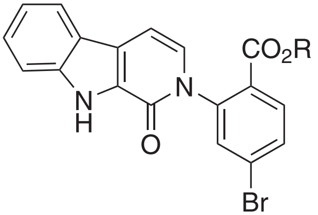
856 $R^1 = H, R^2 = Br$ (3-bromofascaplysin)
859 $R^1 = Br, R^2 = H$ (10-bromofascaplysin)
860 $R^1 = R^2 = Br$ (3,10-bromofascaplysin)



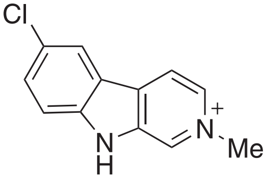
861 R = $COCO_2Me$ (3-bromohomofascaplysin B)
862 R = $COCO_2Et$ (3-bromohomofascaplysin B-1)
863 R = CHO (3-bromohomofascaplysin C)



857 $R^1 = H, R^2 = CO_2Me$ (14-bromoreticulatine)
858 $R^1 = H, R^2 = CO_2$ (14-bromoreticulatate)
864 $R^1 = Br, R^2 = CO_2Me$ (7,14-dibromoreticulatine)
865 $R^1 = H, R^2 = OH$ (14-bromoreticulatol)



866 R = Me (3-bromosecofascaplysin A)
867 R = H (3-bromosecofascaplysin B)



870 (nostocarboline)

Figure 131 Brominated fascaplysin alkaloids **856–867** and nostocarboline **870**.

Didemnum sp., a tunicate that contains the fascaplysin alkaloids **856–867.**

Photo 12: Professor Francis J. Schmitz.

An undescribed thorectid sponge from Saipan contains 7-bromoreticulatine (**868**) and 10-bromohomofascaplysate (**869**), along with 10-bromofascaplysin (**859**)[598] (Figure 132). The absolute configuration of **869** was not established. The fresh water *Nostoc* 78-12A cyanobacterium produces nostocarboline (**870**).[599,600] The New Zealand bryozoan *Pterocella*

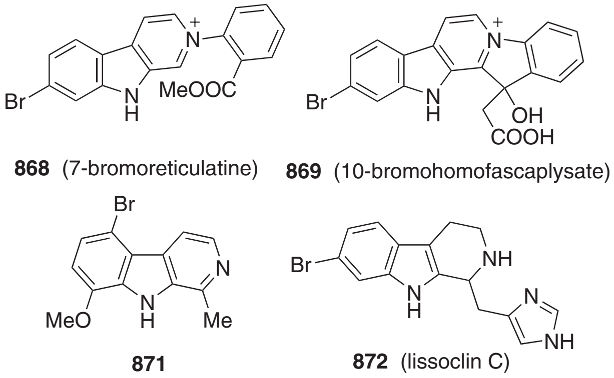


Figure 132 Brominated carboline alkaloids **868–872**.

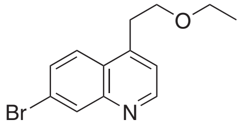
vesiculosa has afforded the new β-carboline alkaloid **871**,[601] and the Great Barrier Reef ascidian *Lissoclinum* sp. contains lissoclin C (**872**), which was isolated in racemic form, in addition to 6-bromotryptamine.[602] Lissoclin C is optically inactive and "probably racemizes during isolation".[602]

G. Quinolines and Other Nitrogen Heterocycles

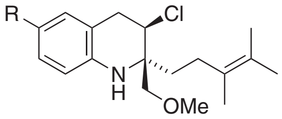
Relatively few examples of halogenated π-deficient aromatic heterocyclic alkaloids are known. Given their extreme unreactivity to electrophilic substitution compared to π-excessive aromatic heterocycles, this is not surprising. Indeed, one of the few examples of a halogenated quinoline alkaloid is 7-bromoquinoline **873**, which was characterized from the marine bryozoan *Flustra foliacea*[603] (Figure 133). Virantmycin (**874**) is produced by *Streptomyces nitrosporeus* and has antibiotic and antiviral properties.[604–607] The corresponding amide, benzastatin C (**875**), is also found in this bacterium.[608,609] The absolute configurations of **874** and **875** were determined from their CD spectra. A marine *Streptomyces* species from a sediment collected off the North Sea coast of Germany has provided mansouramycin B (**876**),[610] and a La Jolla, California, marine *Saccharomonospora* sp. produces the 6-chloroquinoline lodopyridone (**877**).[611]

The Australian ascidian *Aplidium caelestis* contains the novel quinoline carboxylic acids, caelestines A–D (**878–881**)[612] (Figure 134). The sponge *Hyrtios erecta* has furnished quinolones **882** and **883**,[354] and the bryozoan from Palau, *Caulibugula intermis*, contains caulibugulones B (**884**) and C (**885**).[613,614]

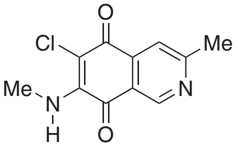
A collection of the cyanobacterium *Lyngbya majuscula* from Puerto Rico has afforded the tetrahydroquinoline glycoside **886**[615] (Figure 135). Three novel tetrahydroquinolines, **887–889**, were isolated from the red alga *Rhodomela confervoides*.[616] An unidentified tunicate from Madagascar has yielded



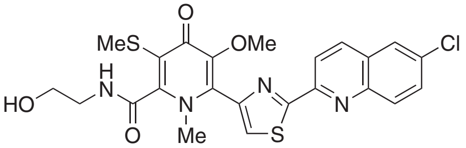
873



874 R = CO_2H (virantmycin)
875 R = $CONH_2$ (benzastatin C)

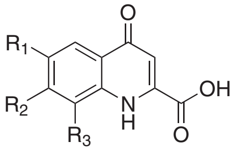


876 (mansouramycin B)

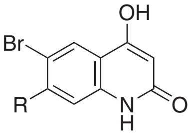


877 (lodopyridone)

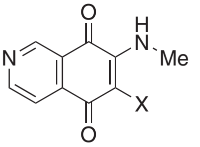
Figure 133 Halogenated alkaloids **873**–**877**.



878 (caelestine A) R_1 = H, R_2 = Br, R_3 = H
879 (caelestine B) R_1 = Br, R_2 = Br, R_3 = H
880 (caelestine C) R_1 = Br, R_2 = H, R_3 = OMe
881 (caelestine D) R_1 = Br, R_2 = Br, R_3 = OMe



882 R = H
883 R = Br

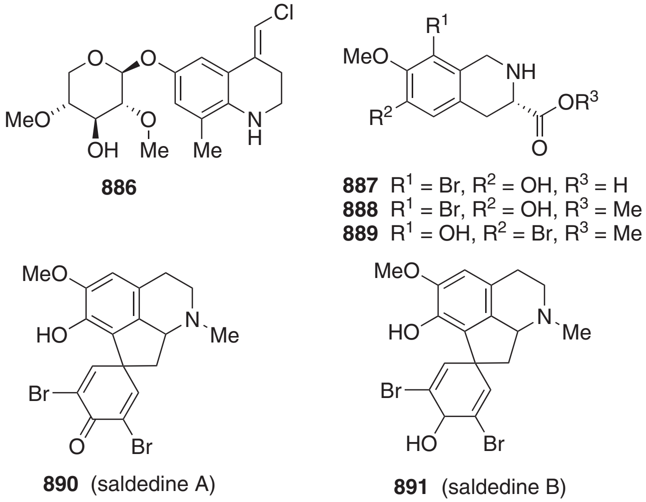


884 X = Br (caulibugulone B)
885 X = Cl (caulibugulone C)

Figure 134 Halogenated alkaloids **878**–**885**.

the first marine proaporphine alkaloids, saldedines A (**890**) and B (**891**).[617] The former was isolated as a racemate while the latter is optically active.

Theoneberine (**892**) was identified in the Okinawan sponge *Theonella* sp.[618] (Figure 136). This alkaloid is the first tetrahydroprotoberberine to be isolated from marine organisms, but its absolute configuration remains



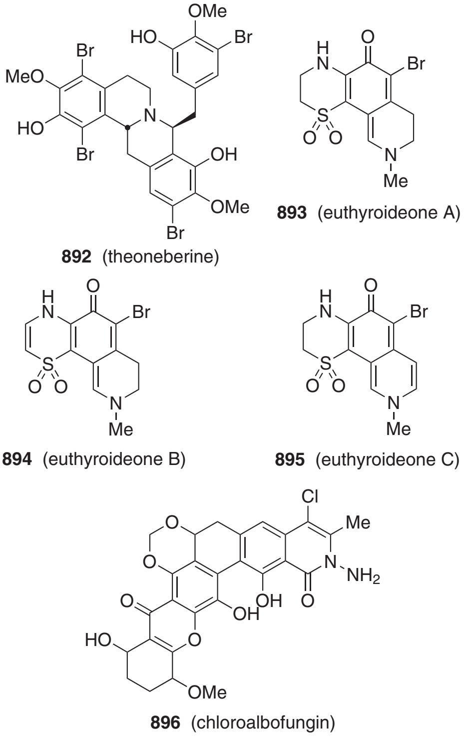
886

887 $R^1 = Br, R^2 = OH, R^3 = H$
888 $R^1 = Br, R^2 = OH, R^3 = Me$
889 $R^1 = OH, R^2 = Br, R^3 = Me$

890 (saldedine A)

891 (saldedine B)

Figure 135 Halogenated alkaloids **886–891**.



892 (theoneberine)

893 (euthyroideone A)

894 (euthyroideone B)

895 (euthyroideone C)

896 (chloroalbofungin)

Figure 136 Halogenated alkaloids **892–896**.

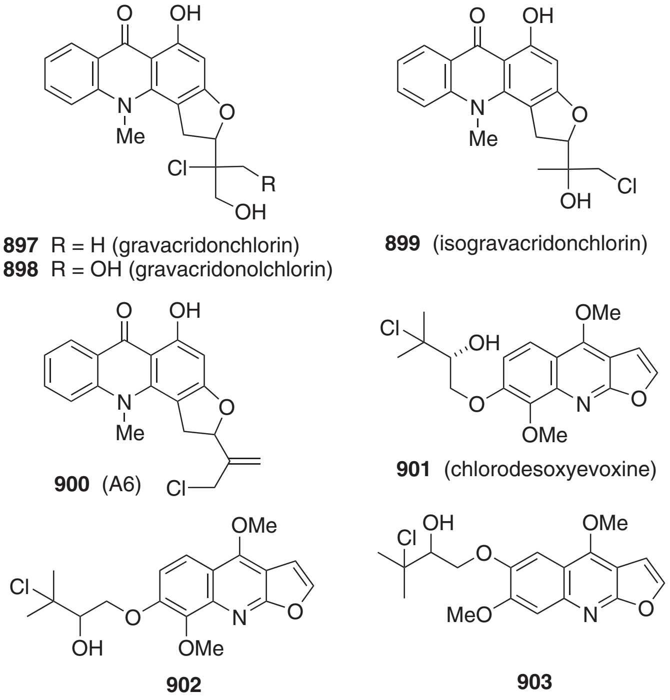
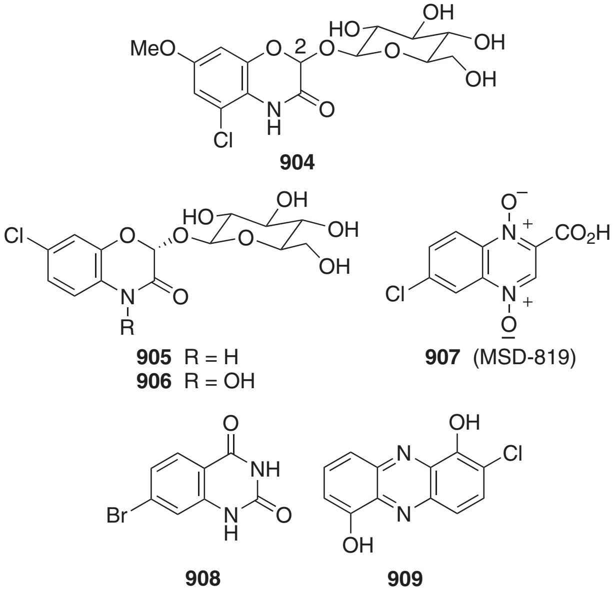


Figure 137 Chlorinated alkaloids **897**–**903**.

to be determined. The New Zealand bryozoan *Euthyroides episcopalis* contains the unusual quinone methides, euthyroideones A–C (**893**–**895**).[619] Chloralbofungin (**896**) is produced by both *Actinomyces albus* and *A. tumemacerans*.[620] The relative stereochemistry of **896** has not been determined.

The novel chlorine-containing acridones gravacridonchlorin (**897**), gravacridonolchlorin (**898**), and isogravacridonchlorin (**899**) were isolated from the roots of *Ruta graveolens*[621,622] (Figure 137). Optical activity and the relative configurations were not reported for these alkaloids. The related A6 (**900**) is found in *R. bracteosa*, *R. macrophylla*, and *R. chalepensis*[623]. When the corresponding allylic alcohol gravacridonol is heated with hydrochloric acid, **900** is not formed, and A6 is not judged to be an isolation artifact. The furoquinoline alkaloid **901** is found in the *Choisya ternata*, a study that determined its absolute configuration.[624] The Surinamese rainforest plant *Ertela* (*Monnieria*) *trifolia* has afforded the related alkaloids **902** and **903**.[625] Both chlorohydrins **902** and **903** are present in the crude extracts and are not considered to be isolation artifacts. An earlier report on the isolation of **903** from the African traditional medicine plant *Teclea nobilis*[626] appears to have been incorrect and, instead, the corresponding diol was isolated.[625]



904

905 R = H
906 R = OH

907 (MSD-819)

908

909

Figure 138 Halogenated alkaloids **904**–**909**.

Benzoxazinoids are important plant metabolites for defense and allelopathy,[627] and several of these alkaloids contain chlorine. Young corn roots (*Zea mays*) contain benzoxazinone **904**; the configuration at C-2 is undefined.[628] The Thai spiny medicinal herb *Acanthus iliciformis* produces **905**[629] (Figure 138), and the *N*-hydroxy analog **906** is found in the medicinal mangrove plant *Acanthus ebracteatus*.[630] The novel quinoxaline 1,4-dioxide MSD-819 (**907**) was isolated from cultures of *Streptomyces ambofaciens*.[631,632] The novel brominated quinazolinedione **908** was found in the tunicate *Pyura sacciformis* along with 7-bromo-3-indolecarbaldehyde (**366**).[633] The broad spectrum antifungal chlorophenazine **909** is produced by the fungus *Streptosporangium* sp.[634]

The auxin inhibitor, 4-chloro-6,7-dimethoxy-2-benzoxazolinone (**910**), is found in *Zea mays*[635] as is the related **911**,[636] which causes growth inhibition of grasses and other plants (Figure 139). The Chinese and Japanese medicinal plant *Houttuyniae cordata* has afforded the new alkaloid 7-chloro-6-demethylcepharadione B (**912**).[637]

The endophytic microfungus *Pestalotiopsis* sp., which grows on wet white rice, has yielded the novel caprolactams, pestalactams A (**913**) and C (**914**)[638] (Figure 140). The Papua New Guinean sponge *Pseudoceratina* sp. contains the novel imidazo–azepine alkaloids ceratamines A (**915**) and B (**916**).[639] The histidine derivative and antitumor active girolline (**917**)

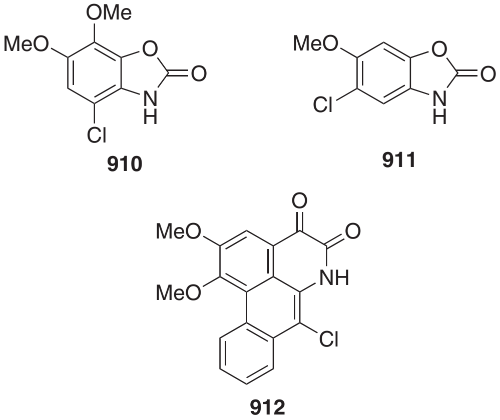


Figure 139 Chlorinated alkaloids **910–912**.

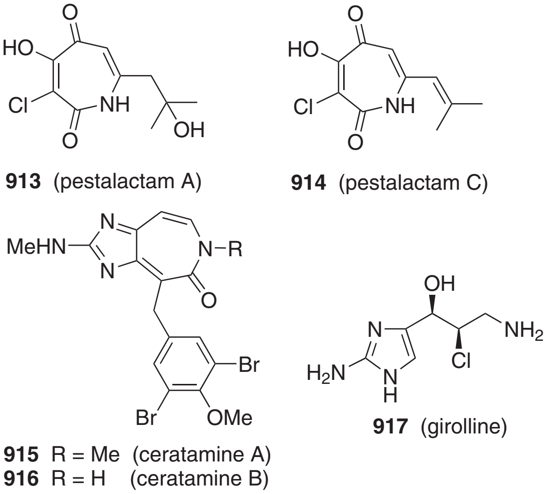
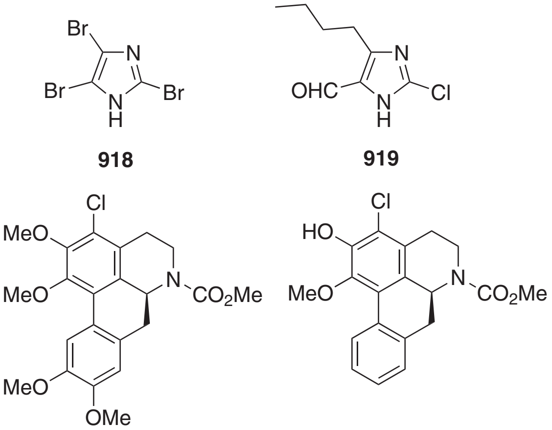


Figure 140 Halogenated alkaloids **913–917**.

occurs in the sponge *Pseudaxinyssa cantharella*,[640] and the *threo* stereochemistry has been established by synthesis[641,642] and X-ray crystallography.[643]

Egg masses of the mollucs *Truncularìopsis trunculus*, *Ceratostoma erinaceum*, and *Trophon geversianus* contain 2,4,5-tribromo-1*H*-imidazole (**918**)[644] (Figure 141). A chlorinated imidazole **919** was isolated from the Indian medicinal plant *Jatropha curcas*.[645] The novel aporphine alkaloids romucosine F (**920**) isolated from *Annona purpurea*[646] and romucosine B (**921**) from *Rollinia mucosa*[647] have antiplatelet aggregation activity. The absolute configuration of **921** is assigned as shown based on known aporphine alkaloids, while the absolute configuration of **920** was not assigned.



918 **919**

920 (romucosine F) **921** (romucosine B)

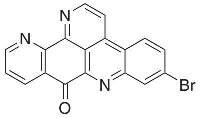
Figure 141 Halogenated alkaloids **918–921**.

The first of a small collection of halogenated pyridoacridine alkaloids is 2-bromoleptoclinidinone (**922**) from a Truk Lagoon ascidian *Leptoclinides* sp.[648,649] (Figure 142). The Southern Australia ascidian *Aplidium pantherinum* contains pantherinine (**923**),[650] and a tunicate *Trididemnum* sp. has yielded shermilamine A (**924**).[651] A *Petrosia* sp. sponge from Belize has afforded petrosamine (**925**),[652] and petrosamine B (**926**) was found in the Australian sponge *Oceanapia* sp.[653] Petrosamine (**925**) was also isolated from a Thai sponge *Petrosia* sp. along with the new 2-bromoamphimedine (**927**).[654]

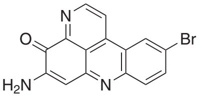
The Australian soil actinomycete *Kibdelosporangium* sp. has yielded several kibdelones[655] and isokibdelones.[656] These include kibdelones A–C (**928–930**) and their corresponding rhamnosides (**931–933**), and 13-oxokibdelone A (**934**),[655] and isokibdelones A–C (**935–937**) and the rhamnoside of A (**938**)[656] (Figures 143 and 144). In this collection of compounds, only the absolute stereochemistry of kibdelone C (**930**) has been established.[657]

Several halogenated purines and pyrimidines are known, some of which are the products of the action of white blood cell myeloperoxidase on foreign DNA, that is, they are the products of inflammation.

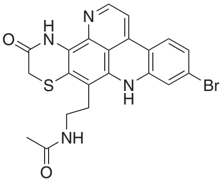
One of the very few natural organofluorine compounds is nucleocidin (**939**) found in the soil microbe *Streptomyces calvus*[658,659] (Figure 145). Chlorosulfonamide AT-625 (**940**) is produced by *Streptomyces rishiriensis*, [660] and ascamycin (**941**) was isolated from another *Streptomyces* sp.[661] The related kumusine (**942**) is found in the Indonesian sponge *Theonella* sp.,[662] and as "trachycladine A" from the Western Australian sponge *Trachycladus laevispirulifer*[663] and the sponge *Theonella cupola*.[664] The red alga *Hypnea valendiae* contains the iodo tubercidin nucleoside (**943**), which is the first natural 5′-deoxyribosyl nucleoside to be identified.[665] The corresponding bromo nucleoside **944** was isolated from the ascidian *Didemnum voeltzkowi*.[666]



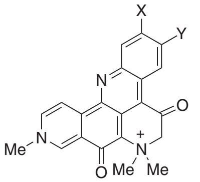
922
(2-bromoleptoclinidinone)



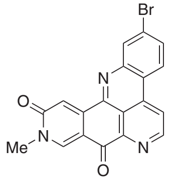
923 (pantherinine)



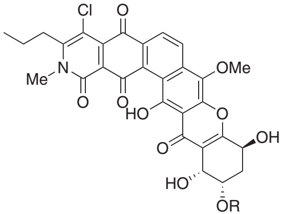
924 (shermilamine A)



925 X = Br, Y = H (petrosamine)
926 X = H, Y = Br (petrosamine B)

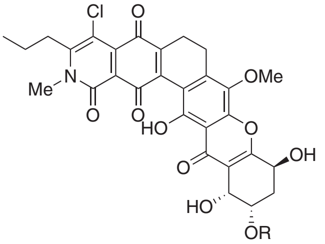


927 (2-bromoamphimedine)

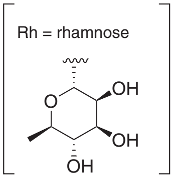


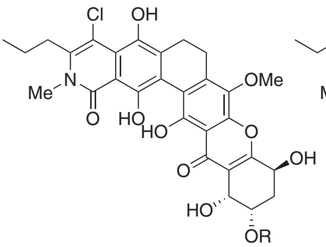
928 R = H (kibdelone A)
931 R = Rh (kibdelone A rhamnoside)

Figure 142 Halogenated alkaloids **922–931**.

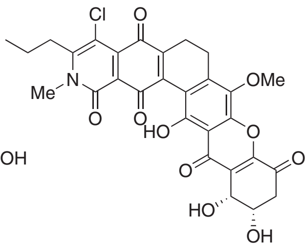


929 R = H (kibdelone B)
932 R = Rh (kibdelone B rhamnoside)



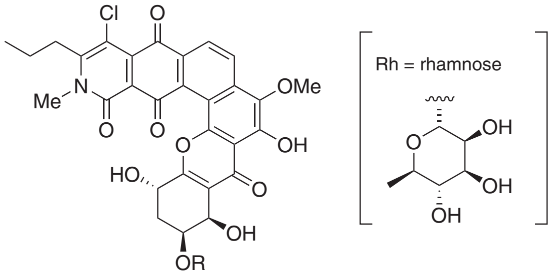


930 R = H (kibdelone C)
933 R = Rh (kibdelone C rhamnoside)

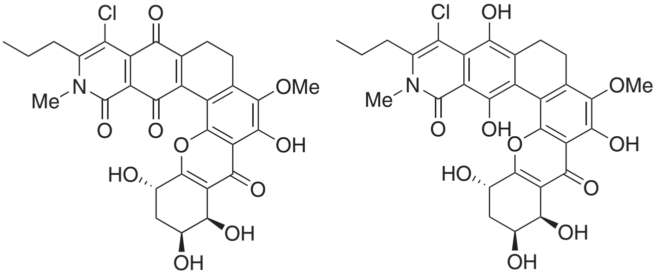


934 (13-oxokibdelone A)

Figure 143 Chlorinated kibdelone alkaloids **929–934**.

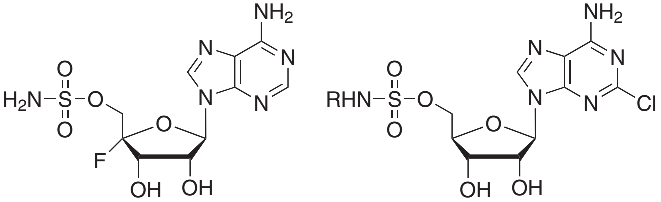


935 R = H (isokibdelone A)
938 R = Rh (isokibdelone A rhamnoside)



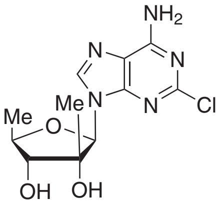
936 (isokibdelone B)   **937** (isokibdelone C)

Figure 144 Chlorinated isokibdelone alkaloids **935–938**.

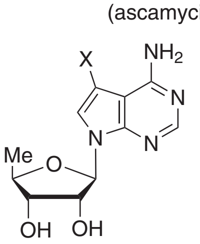


939 (nucleocidin)

940 R = H (AT-625)
941 R = COCH(Me)NH_2 (ascamycin)



942 (kumusine)



943 X = I
944 X = Br

Figure 145 Halogenated nucleoside alkaloids **939–944**.

The novel adenosine deaminase inhibitor 2′-chloropentostatin ("adechlorin") (**945**) was discovered independently in an actinomycete (ATCC 39365)[667] and an *Actinomadura* sp.[668,669] (Figure 146). Salmon sperm contains 5-chlorodeoxycytidine (**946**) and 5-chlorocytosine (**947**),[670] and the marine sponge *Echinodictyum* sp. has produced the brominated pyrrolopyrimidine **948**.[665] The action of myeloperoxidase on human inflammatory tissue produces 5-chlorouracil (**949**),[671,672] 5-bromouracil (**950**),[671,673]

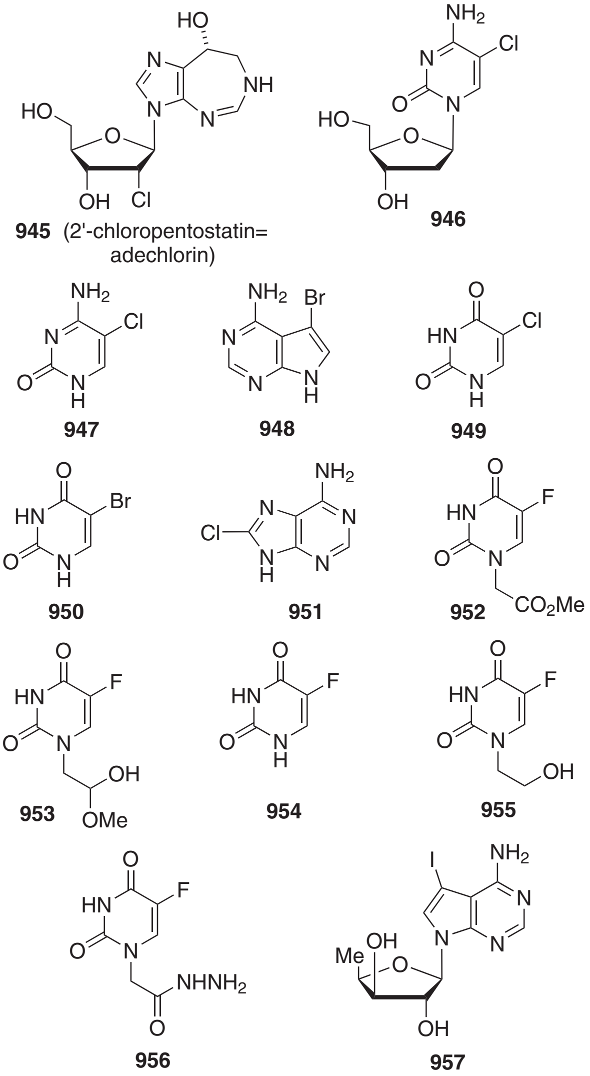
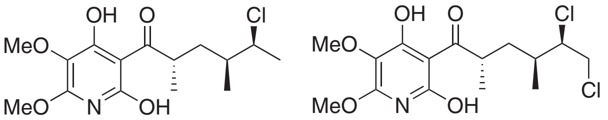


Figure 146 Halogenated nucleic acid alkaloids **945–957**.

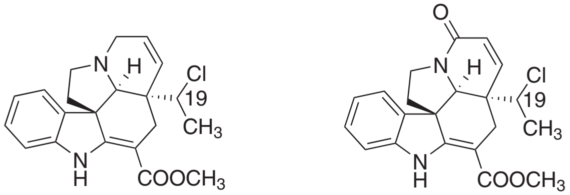
and 8-chloroadenine (**951**),[674] each of which has been isolated from human patients. The sponge *Phakellia fusca* contains five 5-fluorouracil derivatives **952–956**, including the most unusual hemiacetal **953**.[675] The 3′-epimer of **943** (**957**) was isolated from an Okinawan ascidian *Diplosoma* sp.[676]

The novel antifungal antibiotics atpenins A4 (**958**) and A5 (**959**) were found in a culture of *Penicillium* sp.[677] (Figure 147). The chloroalkane side chains are reminiscent of those in WF01-16775 A_1 (**33**) and A_2 (**34**); in fact, atpenin A5 (**959**) may be identical to WF01-16775 A_1 (**33**). The famous periwinkle plant, *Catharanthus roseus*, which produces the clinical anticancer drugs vincristine and vinblastine, is also found to contain the chlorine-containing tabersonine alkaloids **960–963** (absolute configuration).[678] An HPLC examination of the crude extract showed the presence of these alkaloids. The novel phthalazinone azamerone (**964**) was isolated from a marine bacterium related to the genus *Streptomyces*.[679]

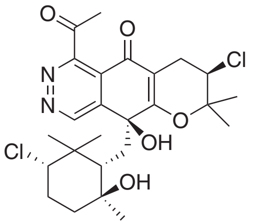
Some of the most amazing examples of natural halogenated alkaloids are the benzodiazepines that are found in humans and in other species,[680–684] including the chlorinated benzodiazepines **965–971** (Figure 148). These alkaloids are produced by plants (wheat grains, potato), and there is evidence of



958 (atpenin A4) **959** (atpenin A5)

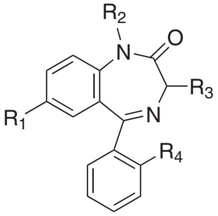


960 (19(*S*)-chlorotabersonine)
961 (19(*R*)-chlorotabersonine)
962 (19(*S*)-chloro-3-oxotabersonine)
963 (19(*R*)-chloro-3-oxotabersonine)



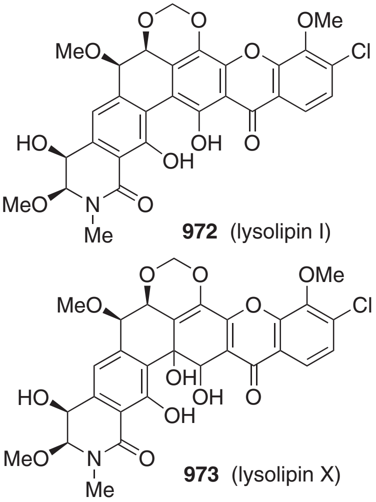
964 (azamerone)

Figure 147 Chlorinated alkaloids **958–964**.



	R$_1$	R$_2$	R$_3$	R$_4$
965	Cl	H	H	H
966	Cl	Me	H	H
967	H	Me	H	Cl
968	Cl	H	OH	Cl
969	Cl	H	H	Cl
970	Cl	Me	OH	Cl
971	Cl	Me	H	Cl

Figure 148 Chlorinated benzodiazepine alkaloids **965–971**.



972 (lysolipin I)

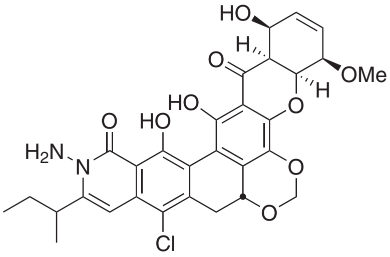
973 (lysolipin X)

Figure 149 Chlorinated lysolipin alkaloids **972–973**.

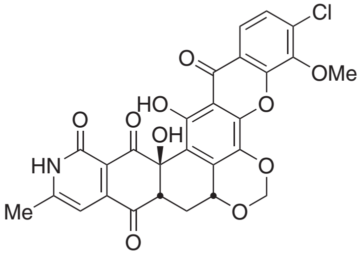
in vivo formation in the mammalian brain.[685–688] Indeed, diazepam (**966**) was discovered in three human brains that were preserved prior to the industrial synthesis of this compound as a minor tranquilizer and antidepressant.[689]

This section concludes with several complex nitrogen-containing natural products that may or may not be categorized as alkaloids but nevertheless are presented here.

The dihydropyridones lysolipins I (**972**) and X (**973**) are produced by *Streptomyces violaceoniger*,[690,691] and their biosynthesis has been pursued[692] (Figure 149). Due to chemical instability of **973**, its diol stereochemistry could not be established. These compounds are similar to chloroalbofungin (**896**) and the kibdelones (e.g., **928**), as are Sch 54445 (**974**) from an *Actinoplanes* sp., which is a potent antifungal agent, [693] and xantholipin (**975**) from a *Streptomyces* sp.[694] (Figure 150). The relative stereochemistry of the *sec*-butyl group in **974** is undefined.



974 (Sch 54445)



975 (xantholipin)

Figure 150 Chlorinated alkaloids **974–975**.

BE-19412A (**976**) is also produced by a Streptomycete[695] as is the piperidine marmycin B (**977**)[696] (Figure 151). The optical properties of **976** were not reported, and the relative configuration of the two stereocenters was not indicated.

A few of the fascinating enediyne antitumor metabolites contain a pyridine or oxazine ring and are considered to be alkaloids. The kedarcidin chromophore **978** is a complex 2-chloropyridine, and the full kedarcidin is from an unidentified actinomycete[697–702] (Figure 152).

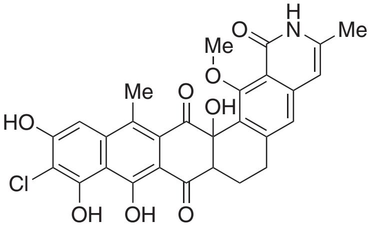
The C-1027 (**979**) and neoC-1027 chromophores (**980**) are closely related oxazinones isolated associated with a protein that was isolated from *Streptomyces globisporus*[703–712] (Figure 153).

Colubricidin A (**981**) is a novel trichloropyrrole macrolide that was isolated from an unidentified *Streptomyces* sp.[713] (Figure 154).

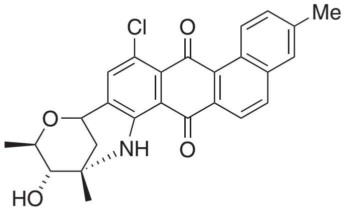
Unfortunately, space does not permit inclusion of the many halogenated indole-containing cyclic peptides and related heterocycle-containing macrolides. However, the large collection of bromotyrosine alkaloids will be covered.

H. Tyrosines

The vast area of halogenated tyrosines is covered herein from 2003 onward, since prior to 2003, the topic was thoroughly covered earlier.[3]

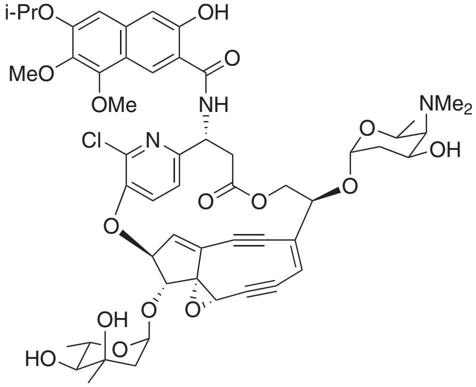


976 (BE-19412A)



977 (marmycin B)

Figure 151 Chlorinated alkaloids **976**–**977**.

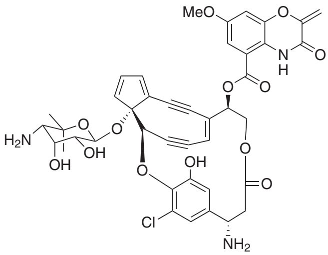


978 (kedarcidin chromophore)

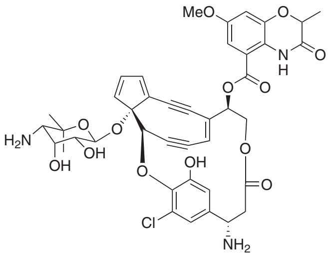
Figure 152 Chlorinated kedarcidin alkaloid chromophore **978**.

1. Simple Tyrosines, Thyroxine, and Related Compounds

Given the myriad natural occurring halogentated phenols,[1,2] it is not surprising that the one phenolic amino acid, tyrosine, is ubiquitous in halogenated form, usually brominated. Whereas nature cannot easily halogenate unactivated benzene rings, phenolic rings are readily halogenated sans catalyst!

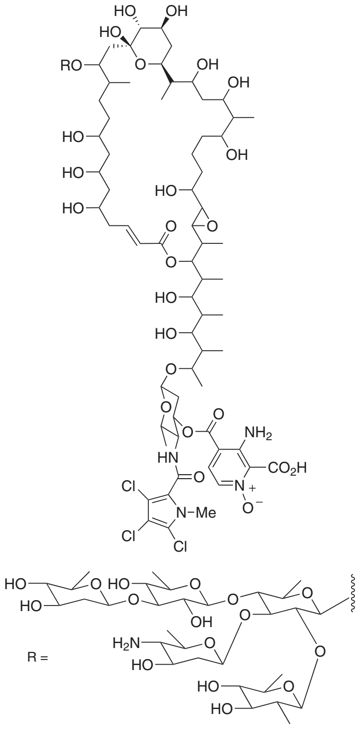


979 (C-1027 chromophore)



980 (neoC-1027 chromophore)

Figure 153 Chlorinated C-1027 chromophore alkaloids **979–980**.



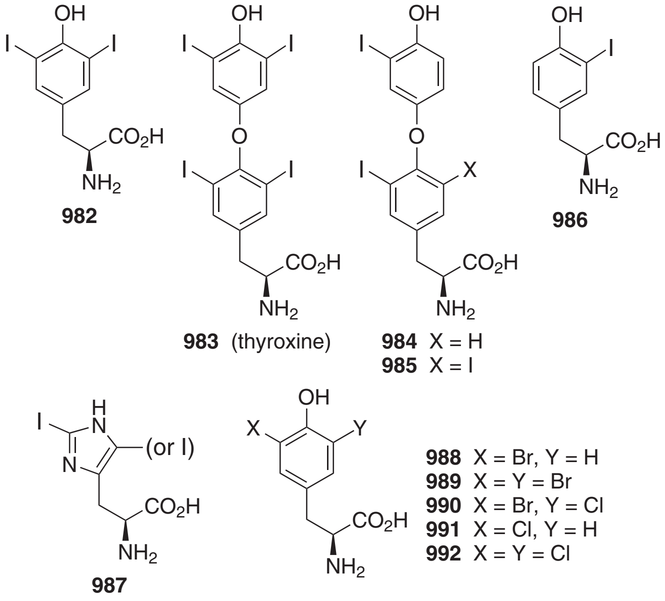
981 (colubricidin A)

Figure 154 Chlorinated colubricidin A alkaloid **981**.

Although iodinated alkaloids are exceedingly rare in nature, some of the oldest and most biologially important of these compounds are iodotyrosines. Indeed, "iodogorgoric acid" (3,5-diiodotyrosine) (**982**) was first isolated >100 years ago from the marine gorgonian *Gorgonia cavolinii*[714] and subsequently characterized[715,716] (Figure 155). Many other early studies identified "iodine" and "bromine" in marine organisms and insects.[717–721] Despite the low abundance of iodide in the ocean (1300 times less than bromide and 380,000 times less than chloride),[1] its facile oxidation allows for its incorporation into organic compounds. During this early period of natural products discovery, thyroxine (**983**) was isolated from the mammalian thyroid gland,[722–724] which also contains **982**[725,726] and 3,3′-diiodothyronine (**984**) and 3,3′,5′-triiodothyronine (**985**).[727] Thyroxines (**983–985**) and/or iodotyrosines (**982**, **986**) are found in sponges,[728–730] ascidians,[720,731–734] gorgonians,[730,735,736] marine algae,[737] and insects.[738,739] Related to the latter is the presence of 2- (or 4-) iodohistidine (**987**) in several insects in addition to iodotyrosines.[739] It is unknown as to which monoiodohistidine was isolated. Bromotyrosines **988** and **989** are present in sponges,[728–730] gorgonians,[730,735] molluscs,[740,741] and insects,[742] the latter typically found within the scleroprotein or cuticle. The mixed 3-bromo-5-chlorotyrosine (**990**) is found in the proteins of the mollusc *Buccinum undatum*[740] and the horseshoe crab (*Limulus polyphemus*).[741] The cuticle of locusts (*Schistocerca gregaria*) is constructed using 3-chlorotyrosine (**991**),[743] and **991** is also present in *Limulus polyphemus*.[741] The scleroprotein of both *Buccinum undatum*[744] and *Limulus polyphemus*[741] contains 3,5-dichlorotyrosine (**992**).

Bromine-containing dityrosines **993** and **994** and trityrosine **995** are embedded in the cuticular proteins of the edible crab (*Cancer pagurus*)[742] (Figure 156). These halogenated tyrosines, which can comprise up to 3% of the amino acids in the scleroproteins,[740] seem to function by increasing the adhesion between individual protein fibers and sheets, thus stabilizing the entire cuticle.[740,742] Novel brominated tyrosines are found in the sponge *Pseudoceratina crassa* (**996–999**),[745] and in the red alga *Rhodomela confervoides* (**1000**).[616]

Mammals also produce 3-chlorotyrosine (**991**) as a product of the myeloperoxidase-hydrogen peroxide–chloride neutrophil system, and this compound is present in red blood cells[746] and albumin.[747] A high concentration of 3-chlorotyrosine occurs in human atherosclerotic tissue,[748] in dialysis patients, as a result of oxidative stress,[749] and in cystic fibrosis patients who have high levels of myeloperoxidase.[750] Infants with chronic lung disease possess high levels of 3-chlorotyrosine, which indicates that myeloperoxidase and neutrophil oxidants contribute to this disease.[751] Similarly, since bromide is present in living systems, both 3-bromotyrosine (**988**) and 3,5-dibromotyrosine (**989**) are products of protein oxidation *in vivo*.[752] This peroxidase oxidation may be involved in asthma tissue damage.[753]



982

983 (thyroxine)

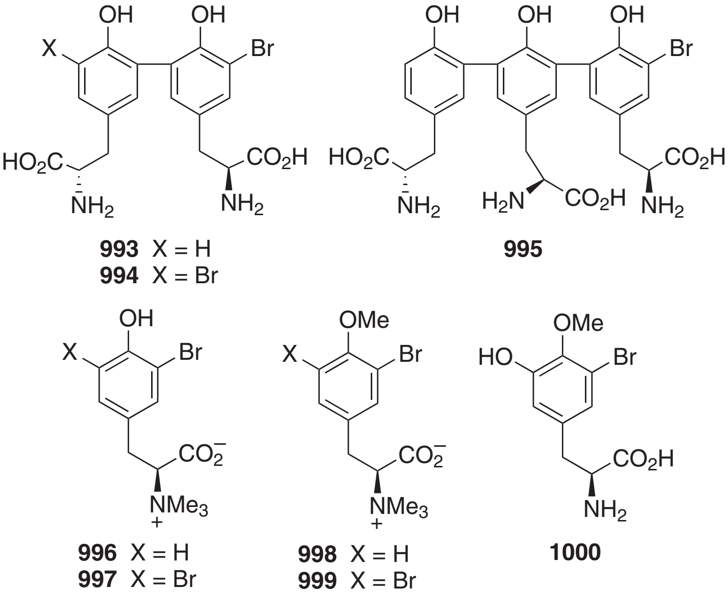
984 X = H
985 X = I

986

987

988 X = Br, Y = H
989 X = Y = Br
990 X = Br, Y = Cl
991 X = Cl, Y = H
992 X = Y = Cl

Figure 155 Halogenated tyrosine alkaloids **982**–**992** and histidine **987**.



993 X = H
994 X = Br

995

996 X = H
997 X = Br

998 X = H
999 X = Br

1000

Figure 156 Bromotyrosine alkaloids **993**–**1000**.

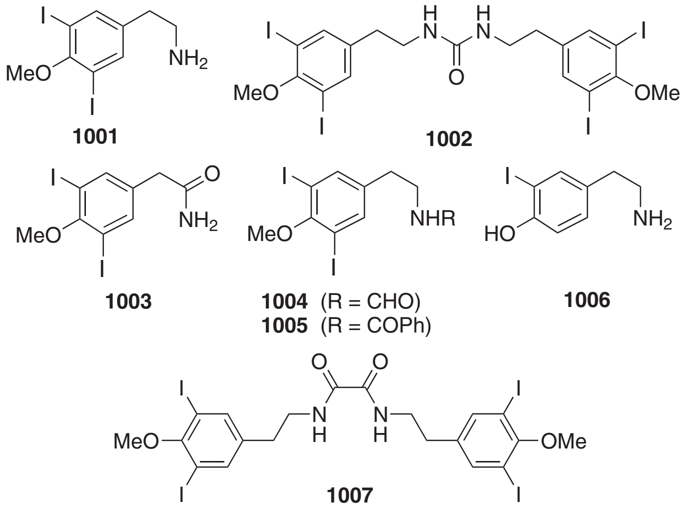


Figure 157 Iodotyramine alkaloids **1001–1007**.

2. Transformed Tyrosines, Tyramines, Phenethylamines, and Related Compounds

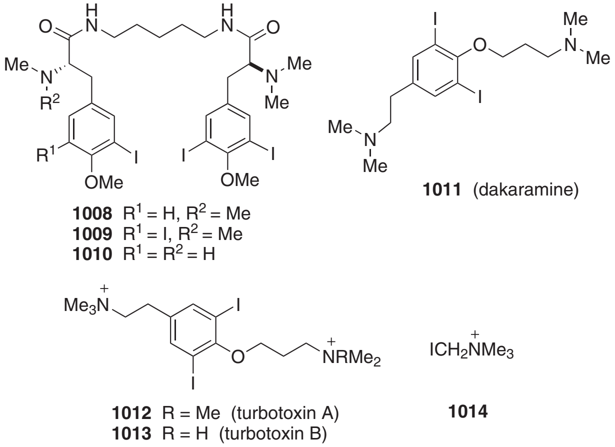
More interesting from a biogenesis standpoint than the simple halogenated tyrosines (*vide supra*) are the "transformed" tyrosines, which are abundant in the marine environment.[1–3] Every effort has been made not to duplicate coverage of the bromotyrosine alkaloids presented in the earlier review.[3]

The novel iodinated alkaloids **1001** and **1002** were isolated from the tunicate *Didemnum* sp.[754] (Figure 157). In addition to containing the protonated and the benzoate salt of diiodo-tyramine **1001**, the ascidian *Didemnum rubeum* also yielded the novel iodo-tyramines **1003–1007**.[755]

A related set of iodinated tyramines, **1008–1010**, was uncovered in the colonial ascidian *Aplidium* sp.[756] (Figure 158). Dakaramine (**1011**) is present in the Senegalese sponge *Ptilocaulis spiculifer*.[757] The highly toxic Japanese gastropod *Turbo marmorata* contains turbotoxins A (**1012**) and B (**1013**), with $LD_{99} = 1\text{–}4$ mg/kg in mice.[758,759] This marine animal also produces the simple iodinated ammonium salt **1014**.[760]

Several newly discovered bromotyramines have been reported in recent years. For example, the New Zealand ascidian *Cnemidocarpa bicornuta* and an Indonesian *Eudistoma* sp. ascidian contain **1015** and **1016**, respectively[761,762] (Figure 159). The *N*-methyl analog of **1015**, 3-bromo-*N*-methyltyramine, is present in the Mediterranean gorgonian *Paramuricea clavata*.[396] The two Brazilian sponges *Aplysina cauliformis* and *Pachychalina* sp. have, respectively, provided dibromophenols **1017** and **1018**.[763] The Red Sea sponge *Suberea mollis* contains subereaphenols A (**1019**)[764] and D

(**1020**).[765] The sponge genus *Pseudoceratina* is a prolific source of bromotyrosine alkaloids,[3] and new entries to this collection are **1021** and **1022** from the Chinese *Pseudoceratina* sp., which are related to the known aeroplysinin-1.[3,766] The related aplysinafulvin (**1023**) was found in *Aplysina fulva* from Brazil and the Southern USA coast.[767]

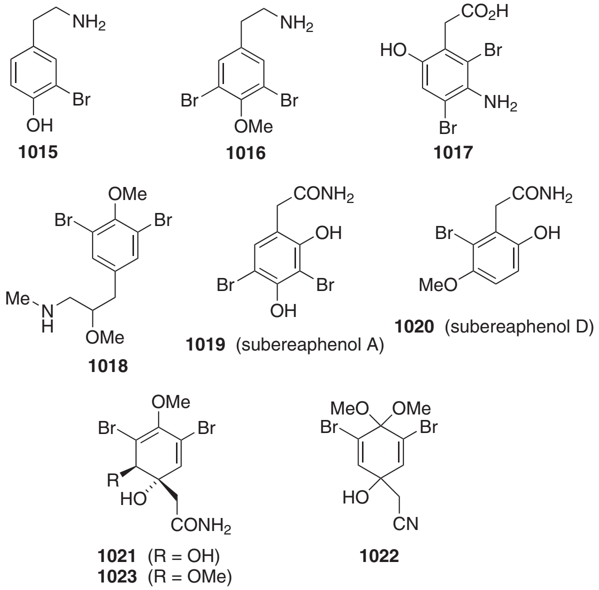

1008 R^1 = H, R^2 = Me
1009 R^1 = I, R^2 = Me
1010 R^1 = R^2 = H

1011 (dakaramine)

1012 R = Me (turbotoxin A)
1013 R = H (turbotoxin B)

1014

Figure 158 Iodotyramine alkaloids **1008–1014**.


1015

1016

1017

1018

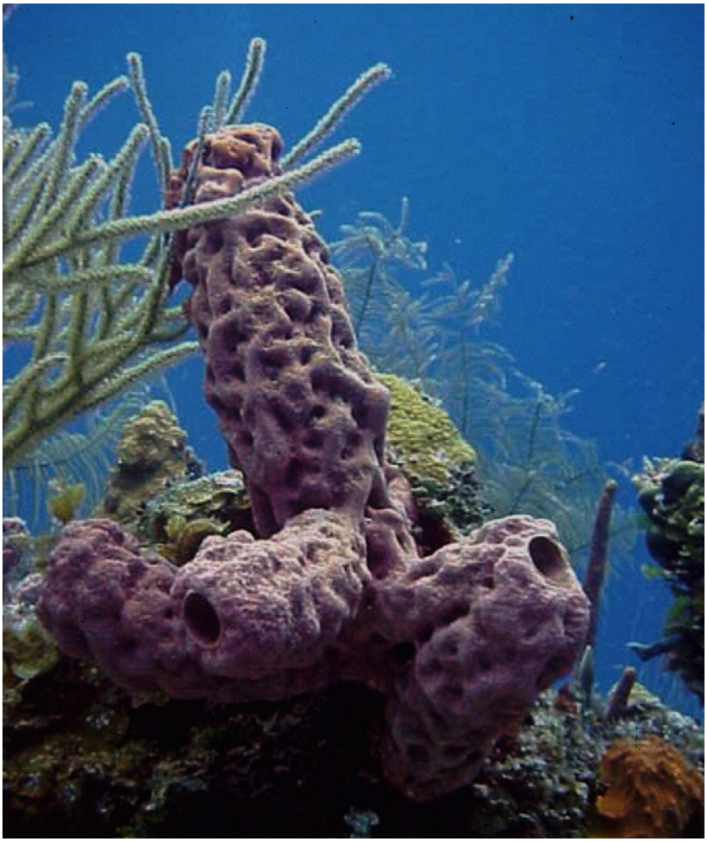
1019 (subereaphenol A)

1020 (subereaphenol D)

1021 (R = OH)
1023 (R = OMe)

1022

Figure 159 Bromotyramine alkaloids **1015–1023**.



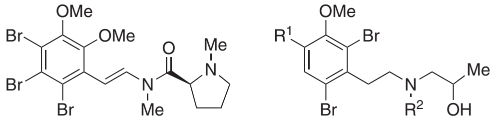
Aplysina archeri, a Caribbean sponge containing several bromotyrosines.

Photo 13: Professor Joseph R. Pawlik.

The prolific bryozoan *Amathia convoluta*, collected in Tasmania, has furnished amathamide G (**1024**),[768] and a Floridian sample of this animal yielded convolutamines A–E (**1025–1029**),[769] F (**1030**), and G (**1031**)[418] (Figure 160). Convolutamine H (**1032**) was isolated from the Tasmanian species.[341]

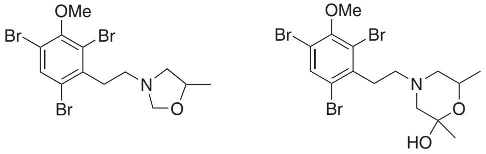
A North Carolinian study of *Amathia convoluta* produced volutamides A–E (**1033–1037**)[770] (Figure 161). The absolute configurations of **1034** and **1035** were established by CD measurements, while those of **1036** and **1037** could not be confidently assigned. Volutamides B and C function as antifeedants toward the pinfish (*Lagodon rhomboids*) and the sea urchin (*Arbacia punctulata*), respectively.[770]

The New Zealand *Amathia wilsoni* contains the novel spirocyclic amathaspiramides A–F (**1038–1043**),[771] and a separate collection of this



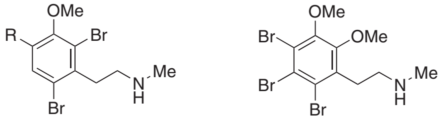
1024 (amathamide G)

1025 R^1 = Br, R^2 = Me (convolutamine A)
1026 R^1 = H, R^2 = Me (convolutamine B)
1027 R^1 = Br, R^2 = H (convolutamine C)



1028 (convolutamine D)

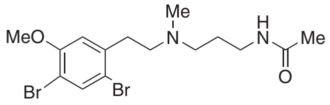
1029 (convolutamine E)



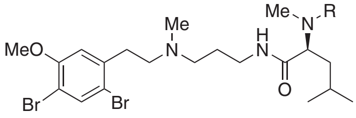
1030 R = Br (convolutamine F)
1031 R = H (convolutamine G)

1032 (convolutamine H)

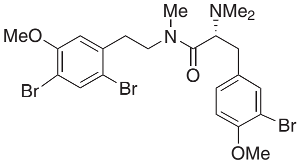
Figure 160 Brominated alkaloids **1024–1032**.



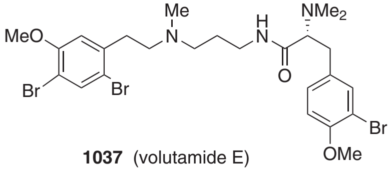
1033 (volutamide A)



1034 R = H (volutamide B)
1035 R = Me (volutamide C)



1036 (volutamide D)



1037 (volutamide E)

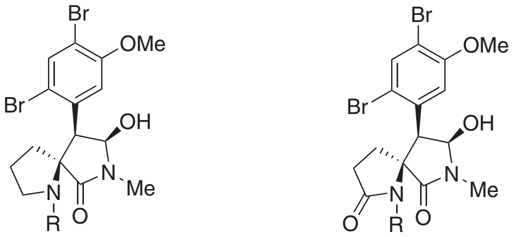
Figure 161 Brominated volutamide alkaloids **1033–1037**.

bryozoan led to the identification of wilsoniamine A (**1044**) and its epimer B (**1045**)[772] (Figure 162).

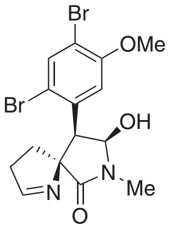
Synoxazolidinones A–C (**1046–1048**), which are rare natural 4-oxazolidinones, are found in the subarctic ascidian *Synoicum pulmonaria*[773,774] (Figure 163).

The sea anemone *Parazoanthus axinellae* contains the hydantoin alkaloids parazoanthines D (**1049**) and E (**1050**)[775] (Figure 164). The novel bromophenols ammonificins A (**1051**) and B (**1052**) are found in the marine bacterium *Thermovibrio ammonificans* living on a deep-sea hydrothermal vent chimney on the East Pacific Rise.[776]

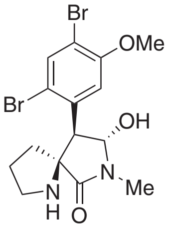
The southern Japanese *Hexadella* sp. sponge has afforded the new moloka'iamines **1053** and **1054** and kuchinoenamine (**1055**), which has



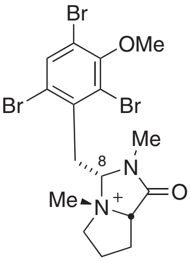
1038 R = Me (amathaspiramide A) **1039** R = Me (amathaspiramide B)
1040 R = H (amathaspiramide C) **1041** R = H (amathaspiramide D)



1042 (amathaspiramide E)



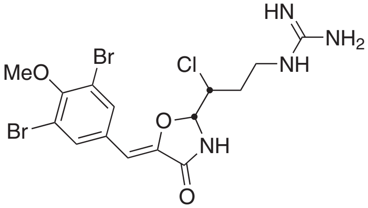
1043 (amathaspiramide F)



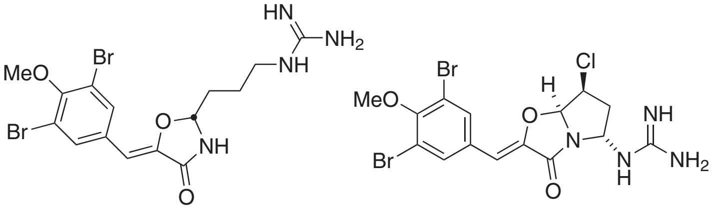
1044 (wilsoniamine A)
1045 (wilsoniamine B) (C-8 epimer)

Figure 162 Brominated amathaspiramide and wilsoniamine alkaloids **1038–1045**.

the unique tricyclo[5.2.1.0^{2,6}]decane ring system[777] (Figure 165). All three of these alkaloids are antibacterial against the fish pathogenic bacterium *Aeromonas hydrophila*. The sponge *Iotrochota purpurea* from Madagascar has yielded itampolins A (**1056**) and B (**1057**), which consist of three separate phenolic rings including D-bromotyrosine.[778]

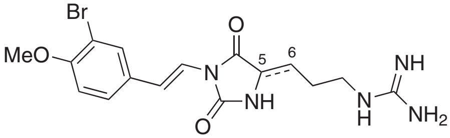


1046 (synoxazolidinone A)

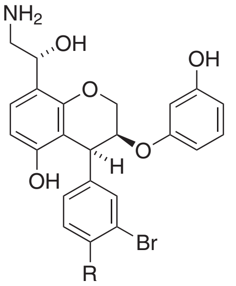


1047 (synoxazolidinone B) **1048** (synoxazolidinone C)

Figure 163 Halogenated synoxazolidinone alkaloids **1046–1048**.

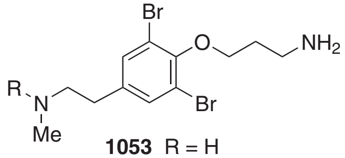


1049 (parazoanthine D)
1050 (parazoanthine E) $\Delta^{5,6}$

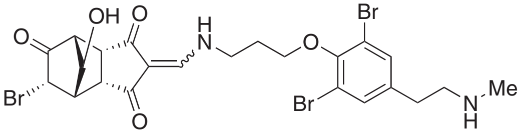


1051 (ammonificin A) R = OH
1052 (ammonificin B) R = Br

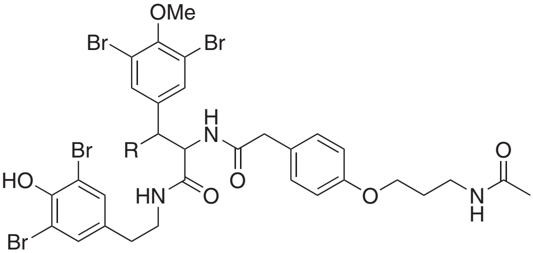
Figure 164 Brominated parazoanthine and ammonificin alkaloids **1049–1052**.



1053 R = H
1054 R = CN



1055 (kuchinoenamine)



1056 R = H (itampolin A)
1057 R = OH (itampolin B)

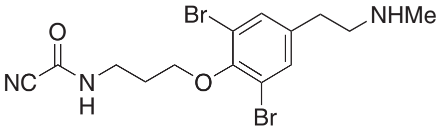
Figure 165 Brominated alkaloids **1053–1057**.

An undescribed Verongid sponge from the Hawaiian island of Molokai has afforded *N*-methylceratinamine (**1058**) and two new moloka'iamines, wai'anaeamines A (**1059**) and B (**1060**)[779] (Figure 166). The related mololipids from this sponge display anti-HIV activity.[3]

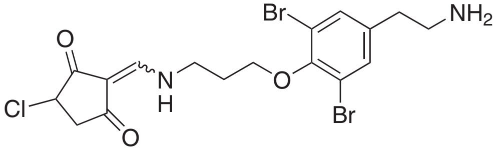
Two collections of the sponge *Psammaplysilla purpurea* from India have yielded **1061**[780] and the new purpurealidins F (**1062**), G (**1063**), and H (**1064**)[781] (Figure 167).

Another sample of *Psammaplysilla* sp. from the Indian Ocean has provided the new psammaplysenes A (**1065**) and B (**1066**), novel alkaloids that inhibit the FOXO1a nuclear export[782] (Figure 168). Psammaplysenes C (**1067**) and D (**1068**) were discovered in an Australian *Psammoclemma* sp. sponge.[783] Aphrocallistin (**1069**) is an unusual adenine-substituted dibromotyrosine alkaloid found in the deep-water Floridan sponge *Aphrocallistes beatrix*.[784]

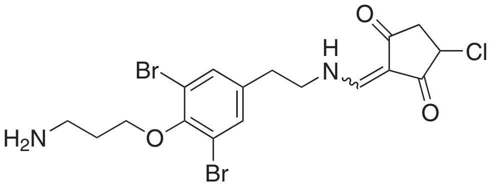
The Red Sea sponge *Pseudoceratina arabica* has produced hydroxymoloka'iamine (**1070**) and moloka'iakitamide (**1071**); both alkaloids possess parasympatholytic effects on isolated rabbit heart and jejunum[785] (Figure 169).



1058 (*N*-methylceratinamine)

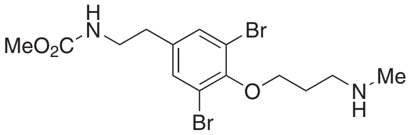


1059 (wai'anaeamine A)

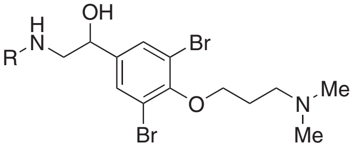


1060 (wai'anaeamine B)

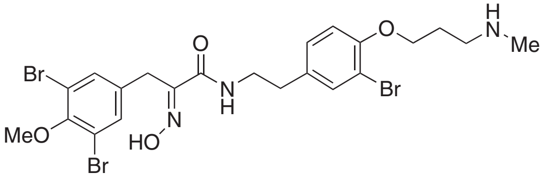
Figure 166 Halogenated alkaloids from Molokai, **1058–1060**.



1061

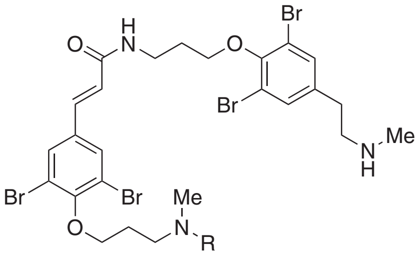


1062 R = H (purpurealidin F)
1063 R = CO_2Et (purpurealidin G)

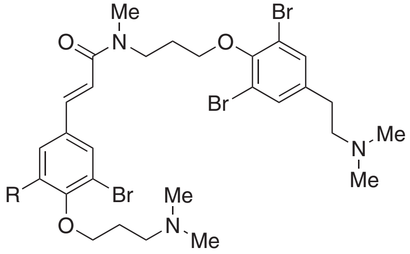


1064 (purpurealidin H)

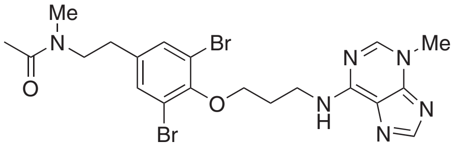
Figure 167 Brominated purpurealidin alkaloids **1061–1064**.



1065 R = Me (psammaplysene A)
1066 R = H (psammaplysene B)

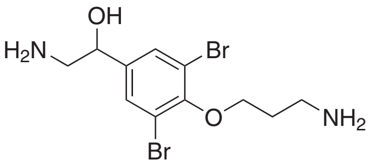


1067 R = H (psammaplysene C)
1068 R = Br (psammaplysene D)

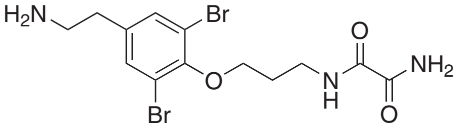


1069 (aphrocallistin)

Figure 168 Brominated psammaplysene alkaloids **1065–1069**.

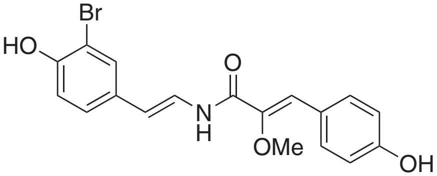


1070 (hydroxymoloka'iamine)

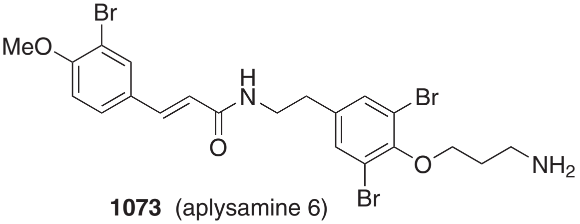


1071 (moloka'iakitamide)

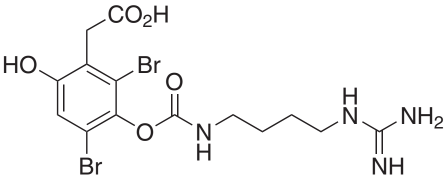
Figure 169 Bromotyrosine alkaloids **1070–1071**.



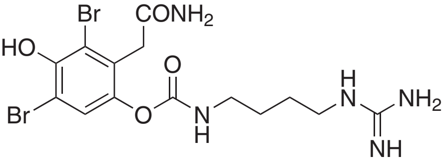
1072 (botryllamide K)



1073 (aplysamine 6)



1074 (clavatadine A)

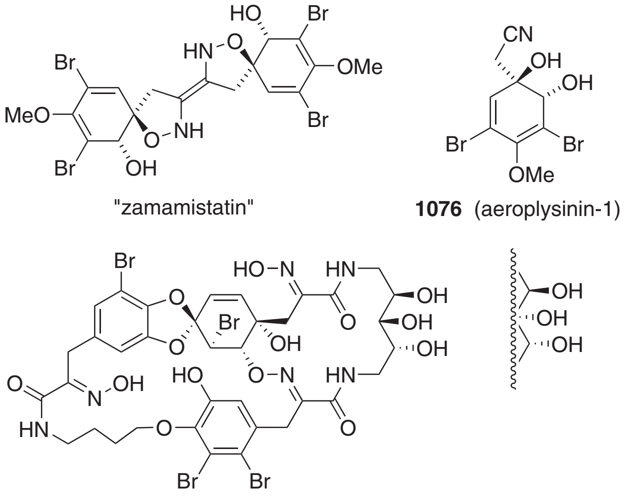


1075 (clavatadine B)

Figure 170 Bromotyrosine alkaloids **1072**–**1075**.

The Australian ascidian *Aplidium altarium* has afforded the new botryllamide K (**1072**),[786] and a new aplysamine, aplysamine 6 (**1073**), was isolated from an Australian *Pseudoceratina* sp. sponge[787] (Figure 170). The Queensland Great Barrier Reef has yielded clavatadines A (**1074**) and B (**1075**) courtesy of the sponge *Suberea clavata*.[788]

An Okinawan collection of *Pseudoceratina purpurea* has produced what was proposed to be a bis-spirocyclic "zamamistatin."[789] However, this structure has found to be the well-known aeroplysinin-1 (**1076**) (two revisions)[790] (Figure 171). A true set of spirocyclic marine alkaloids are pseudoceratins A (**1077**) and B (**1078**), which were found in *Pseudoceratina purpurea*, a sponge in Southern Japan.[791]



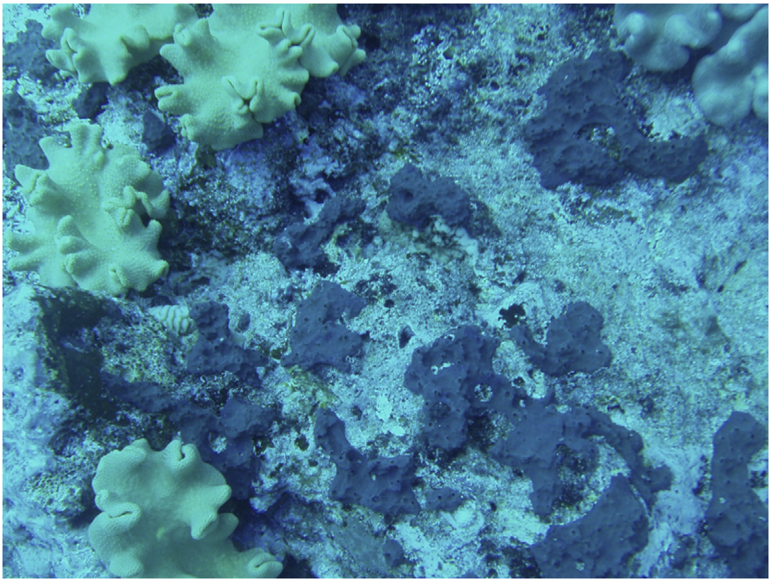
"zamamistatin"

1076 (aeroplysinin-1)

1077 (pseudoceratin A)

1078 (pseudoceratin B)

Figure 171 Brominated alkaloids **1076–1078**.

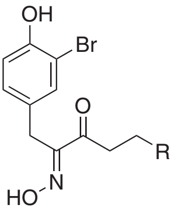


Pseudoceratina purpurea, a sponge that contains the pseudoceratins **1077–1078.**
Photo 14: Professor Phil Crews.

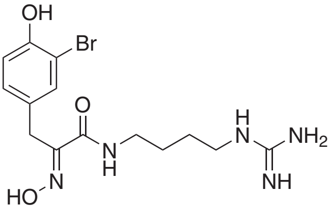
Like the pseudoceratins **1077** and **1078**, numerous bromotyrosine oxime amides are known in the marine environment generally from sponges.[3] New examples include psammaplins M (**1079**), I (**1080**), and B (**1081**) from the twin-sponge association of *Jaspis* sp. and *Poecillastra* sp.,[792] and the related psammaplin N (**1082**) from the Queensland sponge *Aplysinella rhax*[793] (Figure 172). Clavatadine E (**1083**) is found in the previously cited sponge *Suberea clavata*,[794] and JBIR-44 (**1084**) has been isolated from the Okinawan *Psammaplysilla purpurea*.[795]

The novel imidazolyl-quinolone tyrokeradines A (**1085**) and B (**1086**) were characterized from an Okinawan Verongida sponge[796] (Figure 173). Another Okinawan sponge, *Pseudoceratina purpurea*, has yielded 20-*N*-methylpurpuramine E (**1087**),[797] the methylated analog of the previously known purpuramine E.

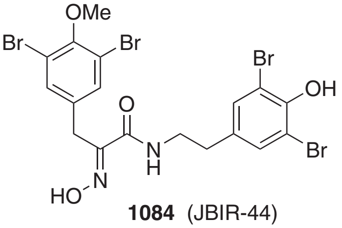
The novel spermine bromotyrosines spermatinamine (**1088**)[798] and pseudoceramines A–D (**1089–1092**)[799] are found in the Australian sponge *Pseudoceratina* sp. and display good antibacterial activity (Figure 174).



1079 R = CO_2Me (psammaplin M)
1080 R = SO_2Me (psammaplin I)
1081 R = SCN (psammaplin B)
1082 R = SOMe (psammaplin N)

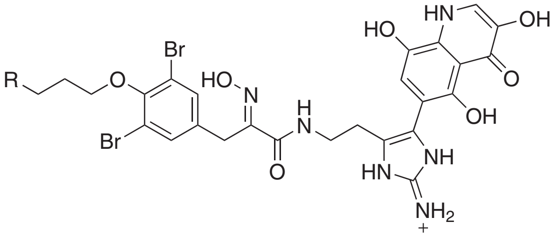


1083 (clavatadine E)



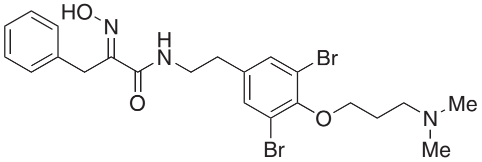
1084 (JBIR-44)

Figure 172 Bromotyrosine alkaloids **1079–1084**.



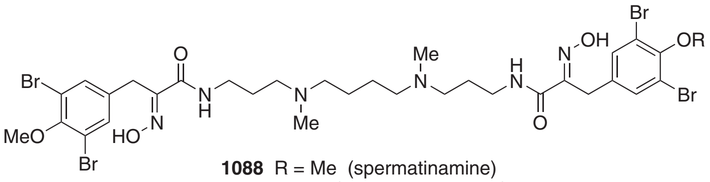
1085 (tyrokeradine A) R = $Me_3\overset{+}{N}$

1086 (tyrokeradine B) R = $H_3\overset{+}{N}$

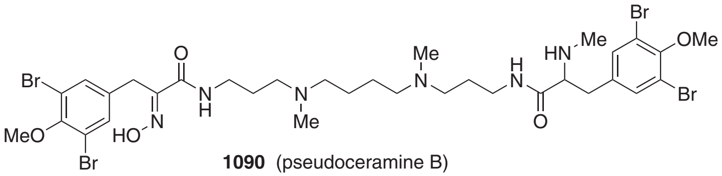


1087 (20-*N*-methylpurpuramine E)

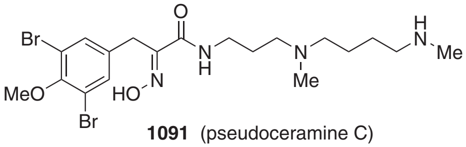
Figure 173 Bromotyrosine alkaloids **1085**–**1087**.



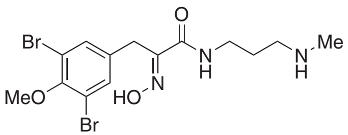
1088 R = Me (spermatinamine)
1089 R = H (pseudoceramine A)



1090 (pseudoceramine B)



1091 (pseudoceramine C)

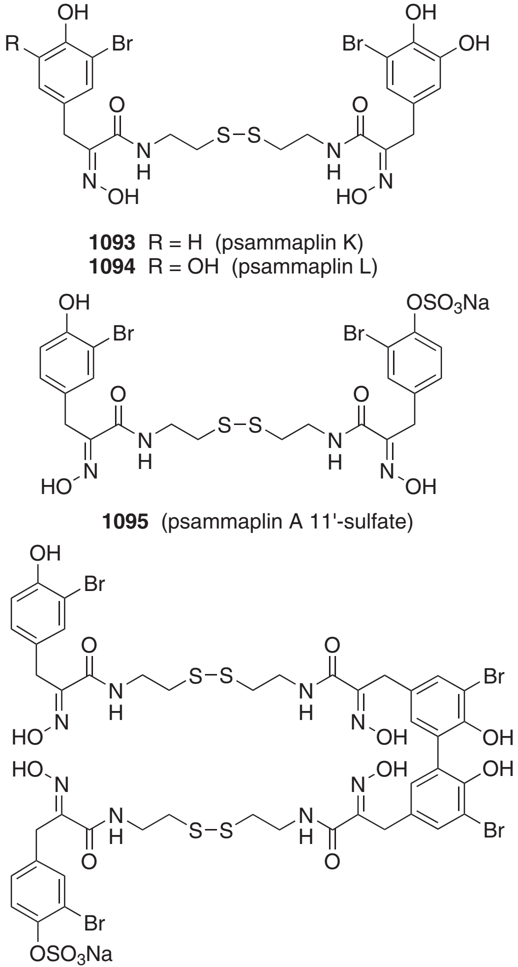


1092 (pseudoceramine D)

Figure 174 Bromotyrosine alkaloids **1088**–**1092**.

New oxime disulfide bromotyrosines have been discovered since the earlier review.[3] Thus, the Fijian sponge *Aplysinella rhax* contains the new psammaplins K (**1093**) and L (**1094**),[800] and an Australian collection of this sponge has afforded psammaplin A 11′-sulfate (**1095**) and bisaprasin 11-sulfate (**1096**),[801] sulfate derivatives of known marine alkaloids[3] (Figure 175).

A very large number of sponge bromotyrosines possess an unprecedented spirocyclohexadiene isoxazoline ring system that derives via a fascinating biosynthesis that has been reviewed.[3]

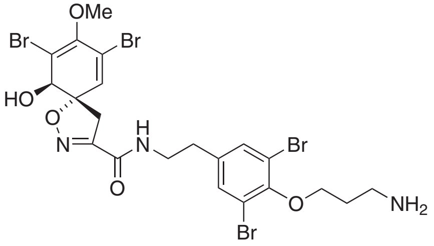


1093 R = H (psammaplin K)
1094 R = OH (psammaplin L)

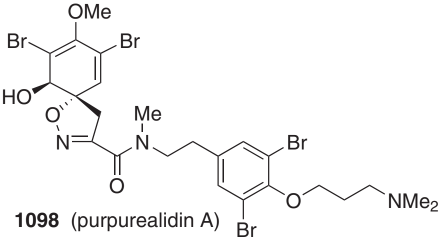
1095 (psammaplin A 11'-sulfate)

1096 (bisaprasin 11'-sulfate)

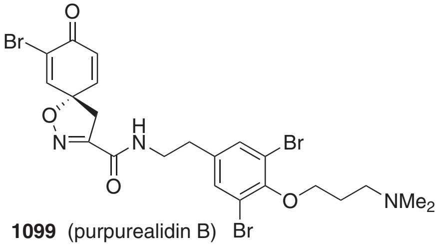
Figure 175 Bromotyrosine psammaplin alkaloids **1093–1096**.



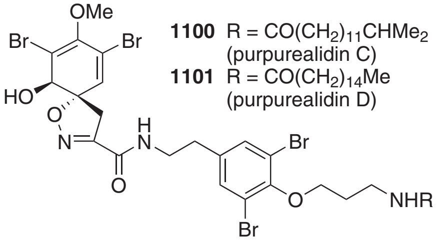
1097 (hexadellin B)



1098 (purpurealidin A)



1099 (purpurealidin B)

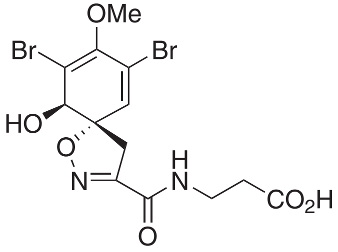


1100 R = $CO(CH_2)_{11}CHMe_2$ (purpurealidin C)
1101 R = $CO(CH_2)_{14}Me$ (purpurealidin D)

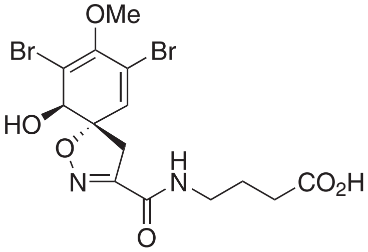
Figure 176 Bromotyrosine hexadellin and purpurealidin alkaloids **1097–1101**.

Hexadellins A and B (**1097**) are present in a *Hexadella* sp. sponge[802]; however, the former alkaloid was previously isolated as araplysillin I from *Psammaplysilla arabica*,[803] so only hexadellin B is a new natural product to this review (Figure 176). The Indian sponge *Psammaplysilla purpurea* contains purpurealidins A–D (**1098–1101**).[781]

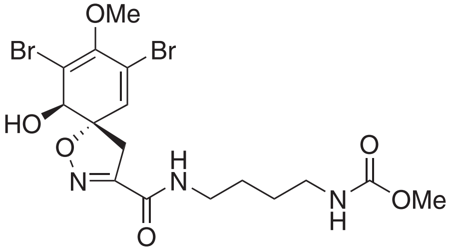
A Gulf of Thailand sponge, *Pseudoceratina purpurea*, produces purpuroceratic acids A (**1102**) and B (**1103**),[804] and the Caribbean sponge *Aplysina insularis* has afforded carbamate **1104**[805] (Figure 177).



1102 (purpuroceratic acid A)



1103 (purpuroceratic acid B)



1104

Figure 177 Bromotyrosine alkaloids **1102–1104**.

Aplysina fistularis, a sponge rich in bromotyrosines.

Photo 15: Dr. Timothy C. Barden.

Clavatadines C (**1105**) and D (**1106**) are found in the Australian sponge *Suberea clavata* and possess the familiar guanidine attachment[794] (Figure 178).

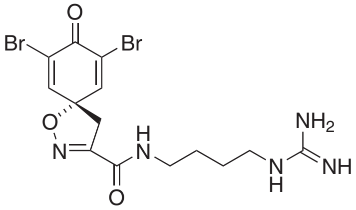
More complex attachments to the amide side chain are seen in ceratinadins A–C (**1107–1109**), which were isolated from the Okinawan sponge *Pseudoceratina* sp.[806] (Figure 179).

Related to carbamate **1104** are the two diethyl carbamates subereamollines A (**1110**) and B (**1111**) isolated from the Red Sea sponge *Suberea mollis*[807] (Figure 180). Carboxylic acid **1112**, which is related to purpuroceratic acid B (**1103**), is found in a Floridian *Aplysina fulva* along with araplysillin *N*^{20}-sulfamate (**1113**).[808] The corresponding 19-hydroxy analog **1114** was discovered in the sponge *Ianthella flabelliformis*.[809] The relative configuration of C-19 was not determined, given very limited alkaloid material. Ianthesine E from the Great Barrier Reef sponge *Pseudoceratina* sp. would seem to be the same as **1113**.[810]

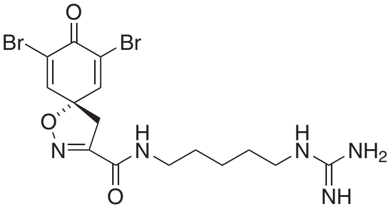
Another study of the sponge *Pseudoceratina* sp. from the South China Sea has yielded purealidins T (**1115**) and U (**1116**)[811] (Figure 181).

Several bis-spirocyclohexadienyl bromotyrosine alkaloids are also known, and in some instances, these sponge metabolites are true dimers.[3] Aplysinillin (**1117**) has been isolated from a Micronesian *Aplysinella* sp. and shows activity against the human breast cancer cell line MCF-7[812] (Figure 182). The Malaysian crinoid *Himerometra magnipinna* contains 12-hydroxyhomoaerothionin (**1118**).[813] An Okinawan Verongida sponge has produced the novel sunabedine (**1119**),[814] and pseudoceratinazole A (not shown) from the Australian sponge *Pseudoceratina* sp. appears to be a diastereomer of sunabedine.[815]

Five new agelocaissarines A1 (**1120**), A2 (**1121**), B1 (**1122**), B2 (**1123**), and caissarine C (**1124**) were characterized in the Brazilian sponge *Aplysina caissara*[816] (Figure 183). The absolute configuration of the spiroxazolidine

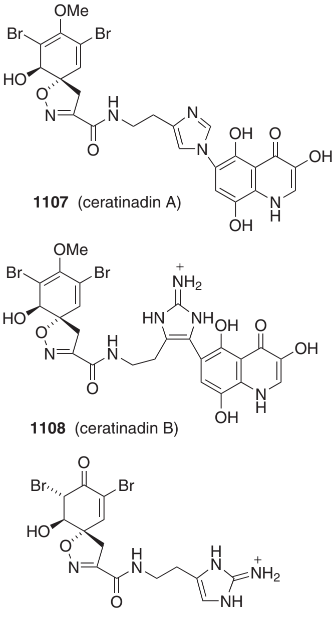


1105 (clavatadine C)



1106 (clavatadine D)

Figure 178 Bromotyrosine clavatadine alkaloids **1105–1106**.

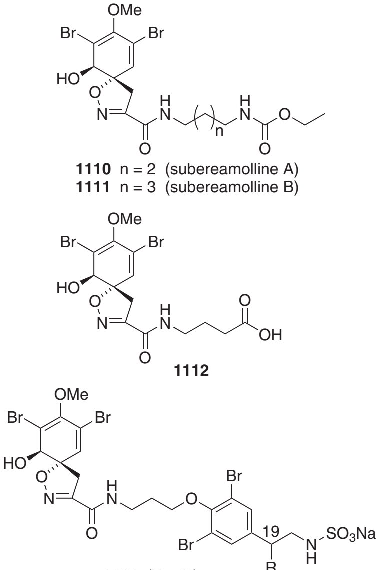


1107 (ceratinadin A)

1108 (ceratinadin B)

1109 (ceratinadin C)

Figure 179 Bromotyrosine ceratinadin alkaloids **1107–1109**.

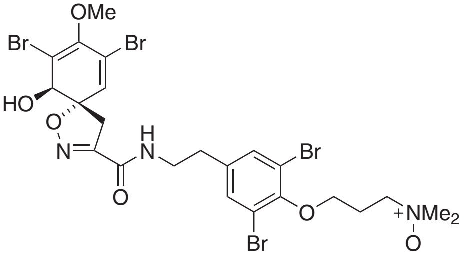


1110 n = 2 (subereamolline A)
1111 n = 3 (subereamolline B)

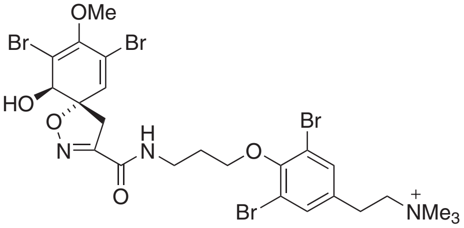
1112

1113 (R = H)
1114 (R = OH)

Figure 180 Bromotyrosine subereamolline and related alkaloids **1110–1114**.

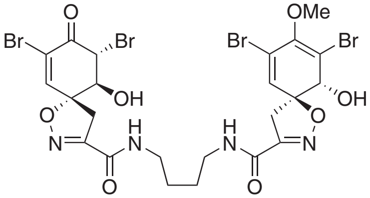


1115 (purealidin T)

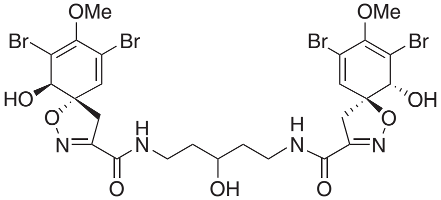


1116 (purealidin U)

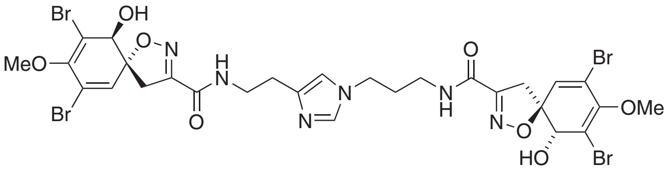
Figure 181 Bromotyrosine purealidin alkaloids **1115–1116**.



1117 (aplysinillin)



1118 (12-hydroxyhomoaerothionin)



1119 (sunabedine)

Figure 182 Bis-bromotyrosine alkaloids **1117–1119**.

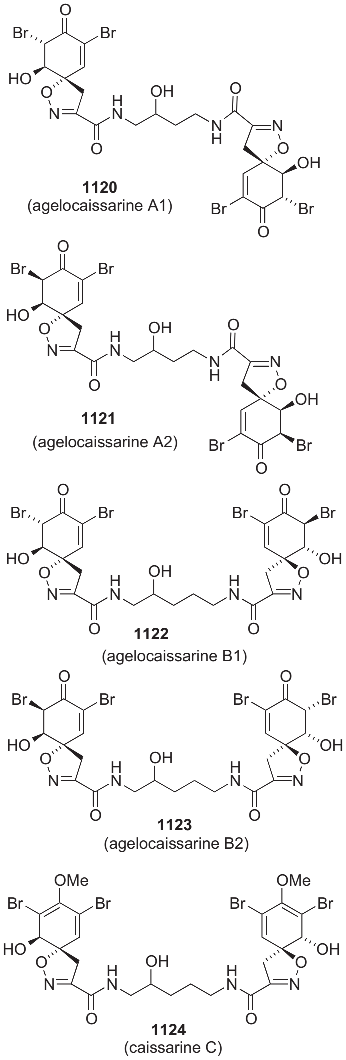


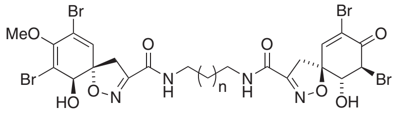
Figure 183 Bromotyrosine agelocaissarine alkaloids **1120–1124**.

moiety of **1124** was established by ^{1}H NMR and circular dichroism analysis, but no attempt was made to determine the absolute stereochemistry at the CHOH center.

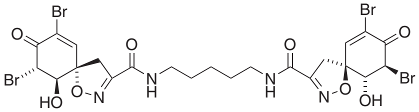
Equally impressive are aplysinones A–D (**1125–1128**) found in *Aplysina gerardogreeni* from the Gulf of California[817] (Figure 184).

An extraordinary class of cyclophanes, called bastadins, consisting of bromotyrosine units have been discovered in various sponges such as genus *Ianthella* found in Australia, Guam, Indonesia, Papua New Guinea, and elsewhere.[3] A study of the previously known bastadins-8, -10, and -12 from the Papua New Guinean sponge *Ianthella basta* has established their absolute configuration.[818]

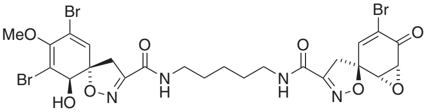
New examples of bastadins include 34-*O*-sulfatobastadin-9 (**1129**) from Guamanian *Ianthella basta*,[819] and bastadins-22 (**1130**) and -23 (**1131**) from the Indian sponge *Dendrilla cactos*[820] (Figure 185).



1125 n = 3 (aplysinone A)
1128 n = 2 (aplysinone D)

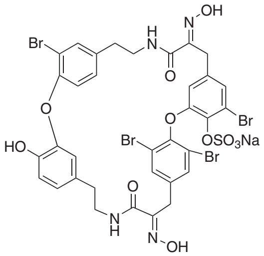


1126 (aplysinone B)

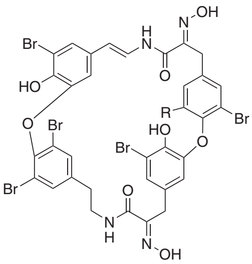


1127 (aplysinone C)

Figure 184 Bromotyrosine aplysinone alkaloids **1125–1128**.



1129 (34-*O*-sulfatobastadin-9)



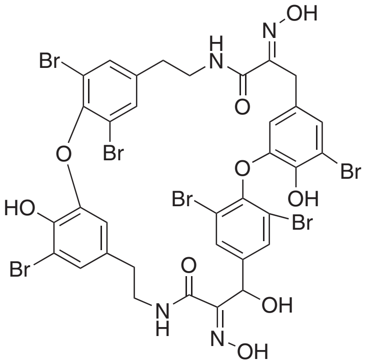
1130 R = Br (bastadin-22)
1131 R = H (bastadin-23)

Figure 185 Bromotyrosine bastadin alkaloids **1129–1131**.

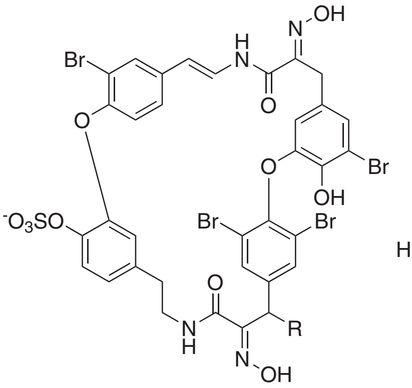
Ianthella basta, a sponge rich in the bastadins.

Photo 16: Professor Francis J. Schmitz.

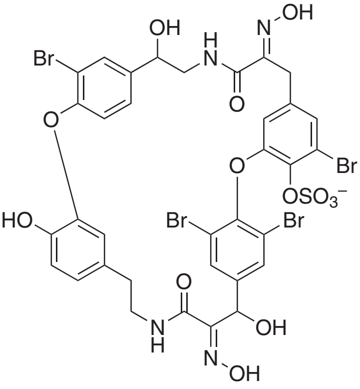
The Australian *Ianthella quadrangulata* contains bastadin-24 (**1132**), which is the 25-hydroxy derivative of bastadin-6[821] (Figure 186). Seven other known bastadins are present in this sponge. *Ianthella flabelliformis*, also collected in Australia, contains bastadin-25 (**1133**), 15-*O*-sulfonabastadin-11 (**1134**), and bastadin-26 (**1135**).[822]



1132 (bastadin-24)



1133 R = OH (bastadin-25)
1134 R = H (15-*O*-sulfonatobastadin 11)



1135 (bastadin-26)

Figure 186 Bromotyrosine bastadin alkaloids **1132–1135**.

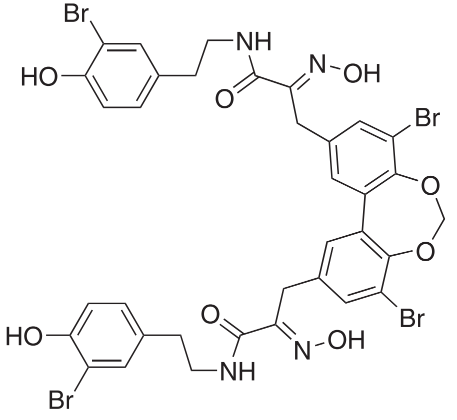
A diastereomer of the known bastadin-19, (*E*,*Z*)-bastadin-19 (not shown) along with the new dioxepine bastadin-3 (**1136**) was isolated from *Ianthella* cf. *reticulata*[823] (Figure 187). Interestingly, the first example of a bastadin-type alkaloid to be found in a seaweed is lithothamnin-A (**1137**) from the red alga *Lithothamnion fragilissimum* in Palau.[824]

A study of the conformations and configurations of the bastadins provides an insight into their different biological activities (antiproliferative and calcium channel modification).[825]

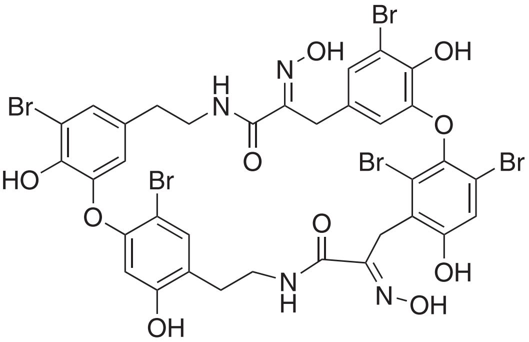
The Australian sponges *Hyattella* sp. and *Pseudoceratina* sp. contain the potent antimalarial psammaplysins G (**1138**) and H (**1139**)[826,827] (Figure 188).

The new bromopyrrole alkaloids, nagelamides O (**1140**) and P (**1141**), and mukanadins E (**1142**) and F (**1143**), were characterized from the sponge *Agelas* sp. in Okinawa[828] (Figure 189).

The Palauan ascidian *Botrylloides tyreum* has furnished the new botryllamide G (**1144**)[829] (Figure 190). The Guamanian collection of the sponge

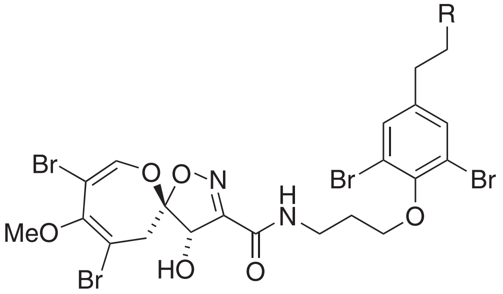


1136 (dioxepine bastadin 3)



1137 (lithothamnin A)

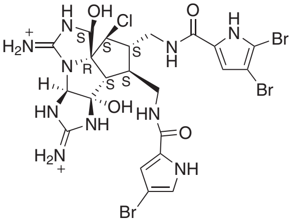
Figure 187 Bromotyrosine bastadin alkaloids **1136–1137**.



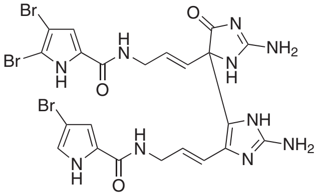
1138 R = N(Me)CONH$_2$ (psammaplysin G)

1139 R = $\overset{+}{\mathrm{N}}\mathrm{Me}_3$ (psammaplysin H)

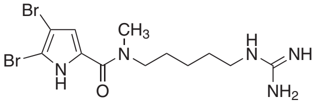
Figure 188 Bromotyrosine psammaplysin alkaloids **1138–1139**.



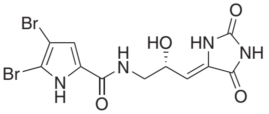
1140 (nagelamide O)



1141 (nagelamide P)

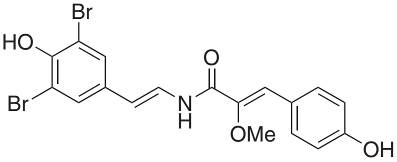


1142 (mukanadin E)

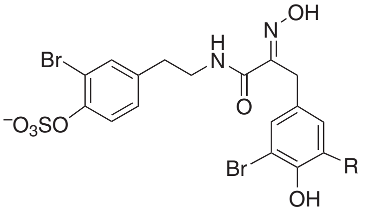


1143 (mukanadin F)

Figure 189 Bromopyrrole alkaloids **1140–1143**.



1144 (botryllamide G)



1145 R = H (1-*O*-sulfatohemibastadin-1)
1146 R = Br (1-*O*-sulfatohemibastadin-2)

Figure 190 Bromotyrosine alkaloids **1144–1146**.

Ianthella basta mentioned earlier also afforded 1-*O*-sulfatohemibastadins-1 (**1145**) and -2 (**1146**).[819]

III. SUMMARY

Once considered to be isolation artifacts or chemical “mistakes” of nature, the number of naturally occurring organohalogen compounds has grown from a dozen in 1954[830] to >5000 today.[831] Of these, at least 25% are halogenated alkaloids. This is not surprising since nitrogen-containing pyrroles, indoles, carbolines, tryptamines, tyrosines, and tyramines are excellent platforms for biohalogenation, particularly in the marine environment where both chloride and bromide are plentiful for biooxidation and subsequent incorporation into these electron-rich substrates.

This review presents the occurrence of all halogenated alkaloids, with the exception of marine bromotyrosines where coverage begins where it left off in volume 61 of *The Alkaloids*.[3] Whereas the biological activity of these extraordinary compounds is briefly cited for some examples, a future volume of *The Alkaloids* will present full coverage of this topic and will also include selected syntheses of halogenated alkaloids.

Natural organohalogens of all types, especially marine and terrestrial halogenated alkaloids, comprise a rapidly expanding class of natural products, in many cases expressing powerful biological activity. This enormous proliferation has several origins: (1) a revitalization of natural product research in a search for new drugs, (2) improved compound characterization methods (multidimensional NMR, high-resolution mass spectrometry), (3) specific enzyme-based and other biological assays, (4) sophisticated collection methods (SCUBA and remote submersibles for deep ocean marine collections), (5) new separation and purification techniques (HPLC and countercurrent separation), (6) a greater appreciation of traditional folk medicine and ethobotany, and (7) marine bacteria and fungi as novel sources of natural products.

Halogenated alkaloids are truly omnipresent in the environment. Indeed, one compound, Q1 (**234**), is ubiquitous in the marine food web and is found in the Inuit from their diet of whale blubber.

Given the fact that of the 500,000 estimated marine organisms[832] – which are the source of most halogenated alkaloids – only a small percentage have been investigated for their chemical content, it is certain that myriad new halogenated alkaloids are awaiting discovery. For example, it is estimated that nearly 4000 species of bryozoans have not been examined for their chemical content. The few species that have been studied contain some extraordinary halogenated alkaloids, such as hinckdentine A (**610**) and the chartellines (**611–613**). Of the estimated 1.5 million species of fungi,[833] secondary metabolites have been characterized from only 5000 species.

The future seems bright for the collector of halogenated alkaloids!

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