Natural Chlorine Updates – No. 14

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I. Introduction

This literature review is the fourteenth in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds, although all new natural organohalogen compounds that have been identified since the last *Updates* are described.

The coverage is approximately from November 2000 through May 2001, with inclusions of earlier material as appropriate.

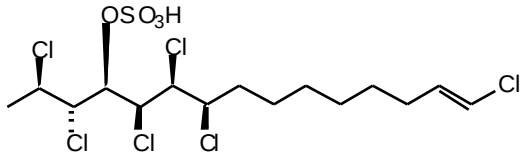
II. New Natural Organohalogens

This *Updates* describes 88 new natural organohalogens, bringing the total number to 3503. Thus, the current breakdown of such naturally produced compounds reported to date is as follows:

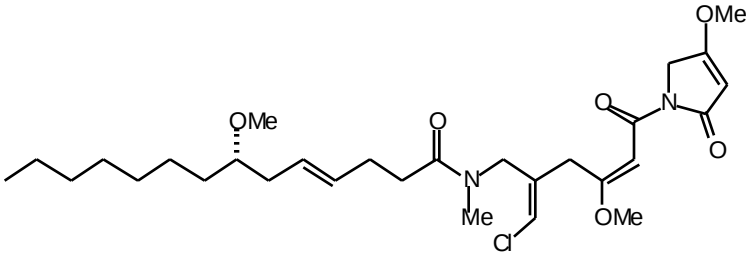
Organochlorine:	2050
Organobromine:	1794
Organoiodine:	95
Organofluorine:	29

As in previous *Updates*, only newly discovered organohalogens are assigned explicit compound numbers (in bold), for ease in counting. Previously known organohalogens are indicated by name or capital letters (in bold).

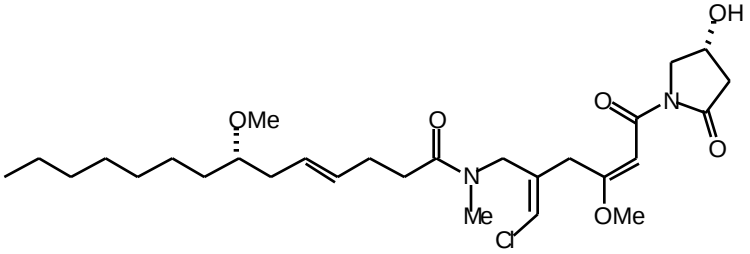
Edible mussels from the Adriatic Sea have yielded the toxic chlorosulfolipid **1** (1). This compound, having the absolute configuration shown, was isolated from the digestive glands of *Mytilus galloprovincialis* and found to be antiproliferative against several cell lines (J774, WEHI164, and P388). Detailed NMR analysis and molecular mechanics calculations led to the structure **1**. The new isomalyngamides A (**2**) and B (**3**) were characterized from the cyanobacterium *Lyngbya majuscula* from Kahala Beach, Oahu, Hawaii (2). Interestingly, the original collection of this organism at this site in 1990 (3) yielded only the isomeric malyngamides A and B, which were not detected in the present study. These new malyngamides are isomeric with malyngamides A and B around the chloromethylene group.



1

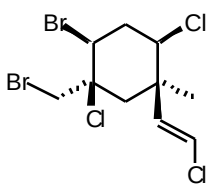


2 (isomalyngamide A)

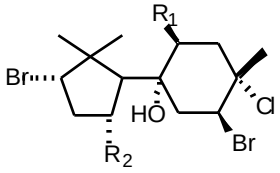


3 (isomalyngamide B)

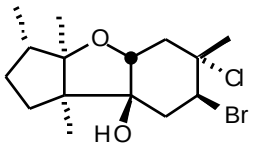
A large number of new halogenated terpenoids have been isolated since the last *Updates*. König *et al.* (4) have isolated eleven known halogenated monoterpenes from several sources of the red alga *Plocamium hamatum*, and reported upon their biological activities. The absolute configuration of metabolite **A** was determined for the first time, and several NMR assignments of halogenated monoterpenes have been revised. The ubiquitous sea hare *Aplysia dactylomela*, collected from South African waters, has yielded the four new halogenated sesquiterpenes algoane (**4**), 1-deacetoxyalgoane (**5**), 1-deacetoxy-8-deoxyalgoane (**6**), and ibhayinol (**7**), in addition to the known *Laurencia* metabolites nidificene and prepacifenol epoxide (5). The absolute configuration of algoane was determined as shown. Another collection of this sea hare has furnished the novel aplydactone (**8**) (absolute configuration) (6). The red seaweed *Laurencia microcladia*, collected off Elba Island, has yielded calenzanol (**9**) containing a novel ring system (7).



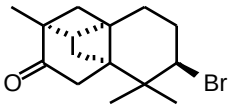
A



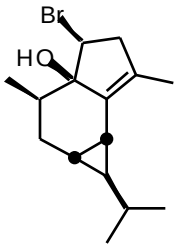
4 $R_1 = OAc, R_2 = OH$ (algoane)
5 $R_1 = H, R_2 = OH$
6 $R_1 = R_2 = H$



7 (ibhayinol)

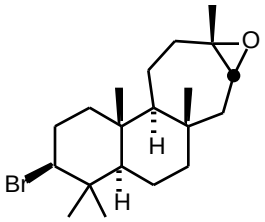


8 (aplydactone)

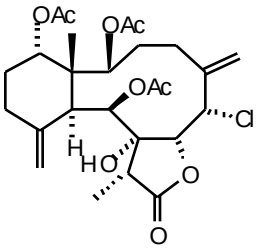


9 (calenzanol)

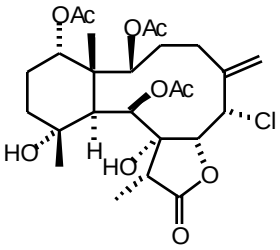
The prolific red algae *Laurencia* (*L. luzonensis*) has afforded the unusual diterpene 3-bromobarekoxide (**10**) (absolute configuration) (8). The gorgonian *Gorgonella umbraculum* has been found to contain the new briarane diterpenes umbraculolides C (**11**) and D (**12**) along with a non-chlorinated analogue (9). The Northern Caribbean gorgonian *Erythropodium caribaeorum* has yielded the new briaranes **13** and **14** (10).



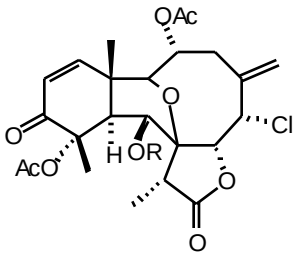
10 (3-bromobarekoxide)



11 (umbraculoide C)

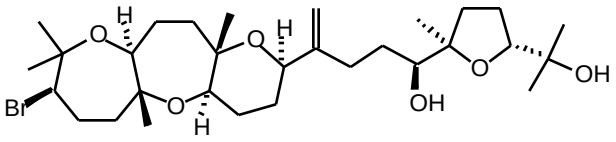


12 (umbraculoide D)

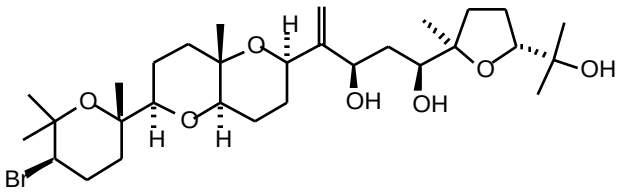


13 R = Ac
14 R = $COCH_2OCO(CH_3)$

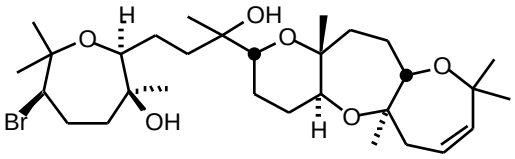
An investigation of *Laurencia viridis* has identified the new squalene-derived triterpenes **15** and **16**, which are related to thyrsiferol (11). The fused cyclic ether rings in **15** are reminescent of those in the brevetoxins and ciguatoxin. Some related bromotriterpene polyethers, armatols A-F (**17**-**22**), were isolated from the Indian Ocean red alga *Chondria armata* (12).



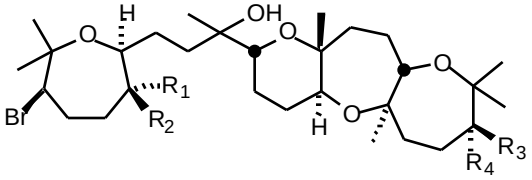
15 (dioxepandehydrothyrsiferol)



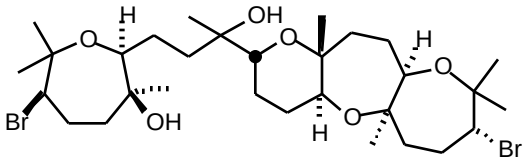
16 (16-epihydroxydehydrothyrsiferol)



17 (armatol A)

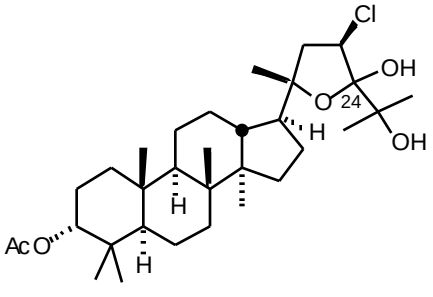


18 R_1 = Me, R_2 = OH, R_3 = H, R_4 = Br (armatol B)
19 R_1 = OH, R_2 = Me, R_3 = H, R_4 = Br (armatol C)
20 R_1 = Me, R_2 = OH, R_3 = Br, R_4 = H (armatol D)
21 R_1 = OH, R_2 = Me, R_3 = Br, R_4 = H (armatol E)

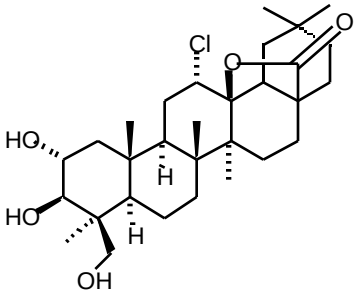


22 (armatol F)

New terrestrial halogenated triterpenoids have also been discovered. The Chinese plant *Amoora yunnanensis* from Yunnan Province contains the dammaranes **23** and **24** (13). The oleanane **25** was isolated as a triacetate from *Mentha villosa* and the detailed proton and carbon NMR spectra were obtained (14). Details of the extraction and isolation are given in a thesis (15).

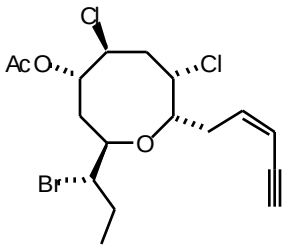


23, 24 (isomeric at C-24)

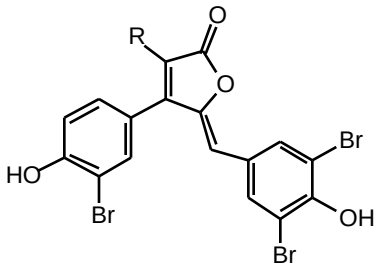


25

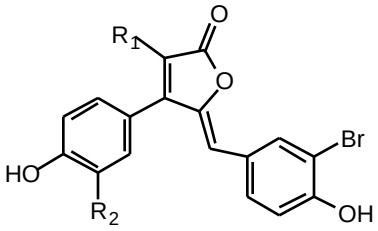
The new laurencienyne B (**26**) has been found in *Laurencia obtusa* along with several known halogenated metabolites (16). This new acetogenin is the *Z*-isomer of the previously known laurencienyne. The ascidian *Synoicum blochmanni* has afforded six new brominated rubrolides **27**-**32**, along with several known analogues (17). Rubrolides I, K, L, and M show significant cytotoxicity against four tumor cell lines (HT-29, MEL-28, P-388, A-549), with rubrolide M showing the greatest activity (ED_{50} = 1.2 µg/mL).



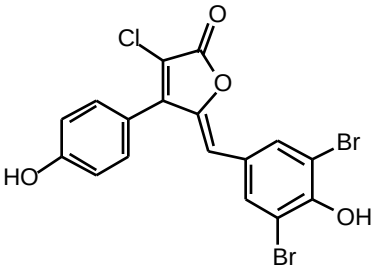
26 (laurencienyne B)



27 R = Cl (rubrolide I)
28 R = H (rubrolide J)

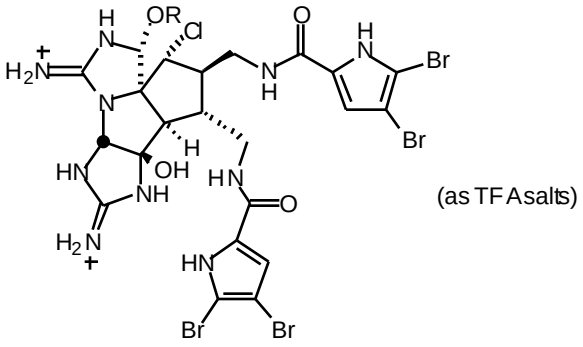


29 R_1 = Cl, R_2 = Br (rubrolide K)
30 R_1 = Cl, R_2 = H (rubrolide M)
31 R_1 = Br, R_2 = Cl (rubrolide N)



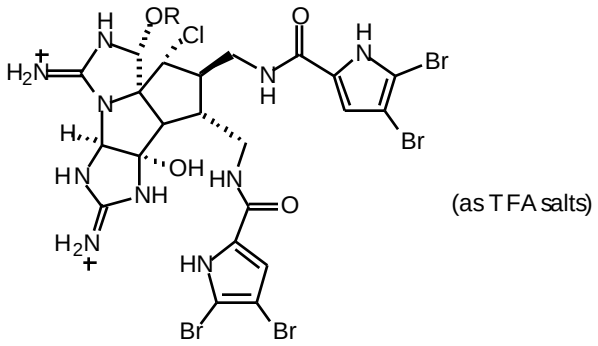
32 (rubrolide L)

Novel halogenated pyrroles continue to be discovered in marine sponges. The Australian *Axinella* sp. has furnished the complex axinellamines A-D (**33**-**36**) (18), and the Mediterranean sponge *Agelas oroides* contains cyclooroidin (**37**) and taurodispacamide A (**38**) (19). Somewhat earlier, a study of the sponge *Pseudaxinyssa cantharella* from New Caledonia revealed the presence of the new metabolites dibromocantharelline (**39**), odiline (**40**) and **41** (20).



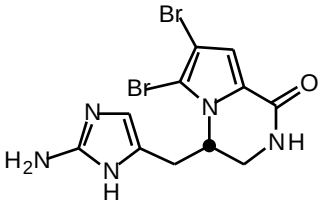
(as TFA salts)

33 R = H (axinellamine A)
34 R = Me (axinellamine C)

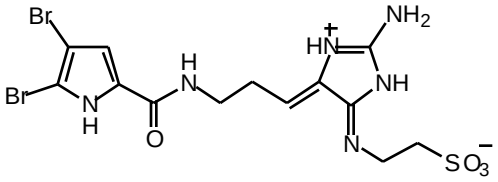


(as TFA salts)

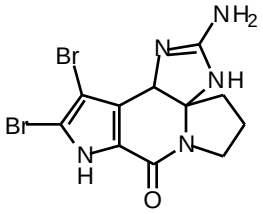
35 R = H (axinellamine B)
36 R = Me (axinellamine D)



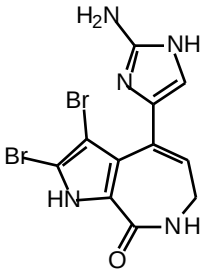
37 (cycloorоidin)



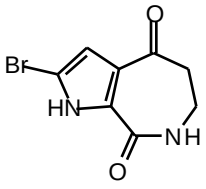
38 (taurodispacamide A)



39 (dibromocantharelline)

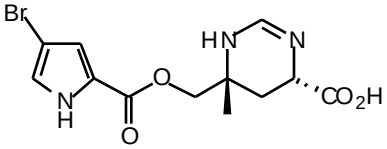


40 (odiline)

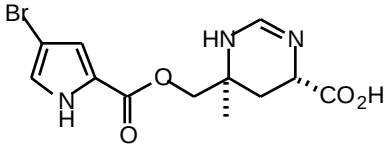


41

The absolute configurations of the previously isolated manzacidins A and C have been determined by total synthesis (21).



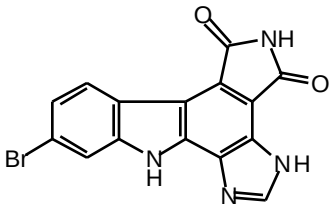
manzacidin A



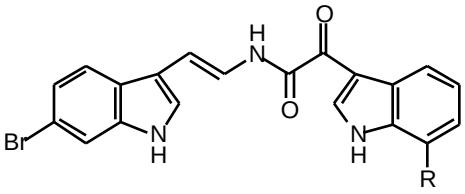
manzacidin C

Several novel halogenated indole metabolites have been recently discovered in marine organisms. The Brazilian ascidian *Didemnum granulatum* has yielded 6-bromogranulatimide (**42**) along with the debromo analogue (22). Coscinamides A (**43**) and C (**44**) were characterized from the sponge *Coscinoderma* sp., along with the non-halogenated coscinamide B (23). A study of the

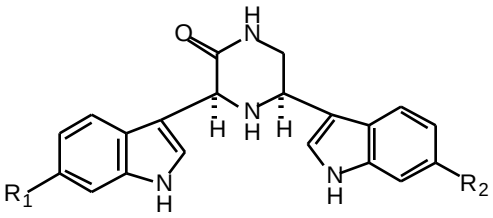
sponge *Rhaphisia lacazei* has afforded 13 bisindole alkaloids including seven new brominated compounds **45-51** related to topsentin and hamacanthin (24). This same Italian group has isolated dragmacidin F (**52**) from the Mediterranean sponge *Halicortex* sp. (25).



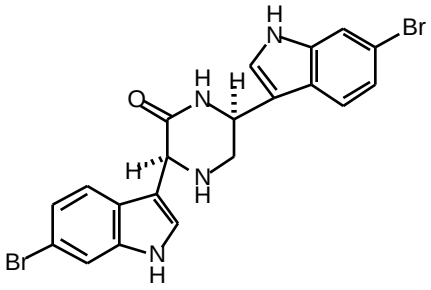
42 (6-bromogranulatimide)



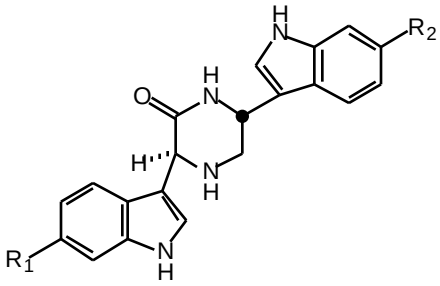
43 R = H (coscinamide A)
44 R = OH (coscinamide C)



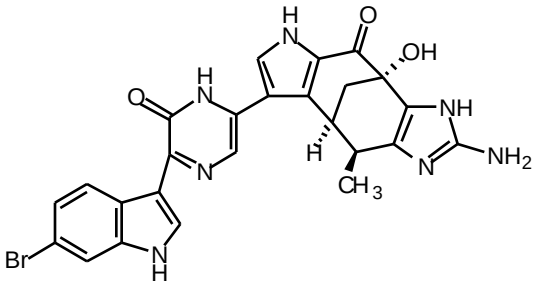
45 $R_1 = R_2 = Br$
46 $R_1 = H, R_2 = Br$
47 $R_1 = Br, R_2 = H$



48

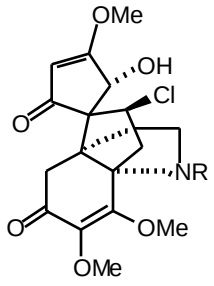


49 $R_1 = R_2 = Br$
50 $R_1 = H, R_2 = Br$
51 $R_1 = Br, R_2 = H$

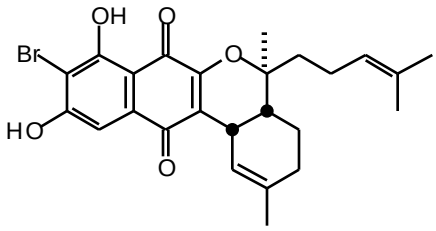


52 (dragmacidin F)

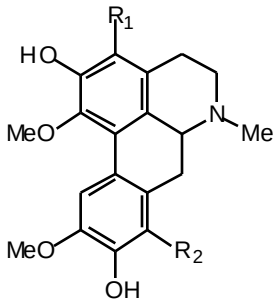
The chlorinated alkaloids dauricumine (**53**) and dauricumidine (**54**), which are isomers of the previously isolated acutumine and acutumidine, were characterized in plant cultures of *Menispermum dauricum* (26). The authors provide evidence as to the biosynthetic relationship of these four alkaloids. Interestingly, the halogenated derivatives **B** of the alkaloid boldine have enhanced monoamine receptor selectively over the alkaloid itself (27). This increased activity is thought to result from enhanced lipophilicity. A marine bacterium has yielded isomarinone (**55**), a bromine ring isomer of the previously isolated marinone from the same bacterial strain (28).



53 R = Me (dauricumine)
54 R = H (dauricumidine)

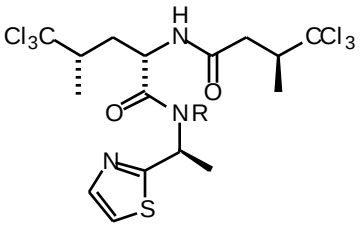


55 (isomarinone)

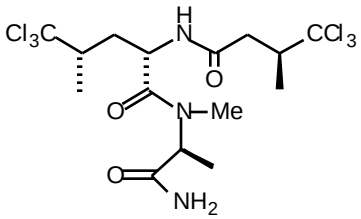


B R_1 = Cl, Br, I; R_2 = Cl, Br

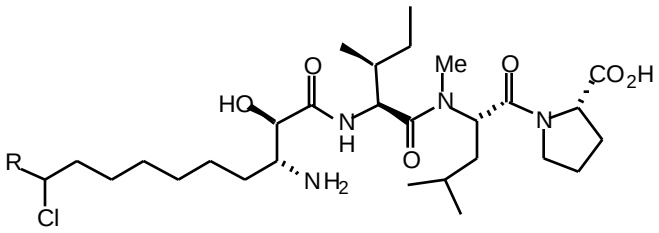
The first isolation of dysidenin-like compounds from a free-living cyanobacterium (*Lyngbya majuscula*) has been reported and has led to the new pseudodysidenin (**56**), nordysidenin (**57**), and dysidenamide (**58**) (29). Four new chlorinated microginins, **59**-**62**, have been isolated from the cyanobacterium *Microcystis aeruginosa* (30). Some of these compounds have inhibitory activity against aminopeptidase M and angiotensin-converting enzyme. In a related investigation it was established by total synthesis that the non-chlorinated aeruginosin 298 A incorporates a D-leucine and not an L-leucine as originally reported (31).



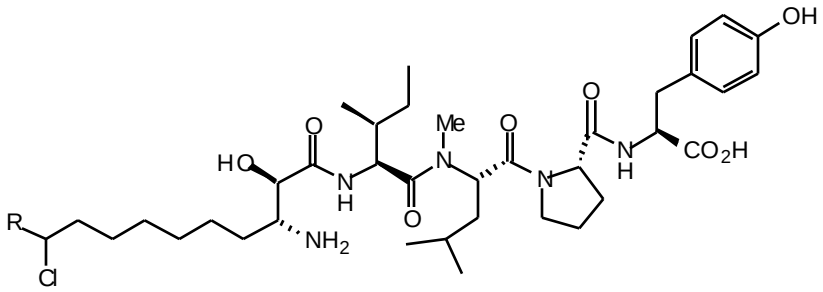
56 R = Me (pseudodysidenin)
57 R = H (nordysidenin)



58 (dysidenamide)

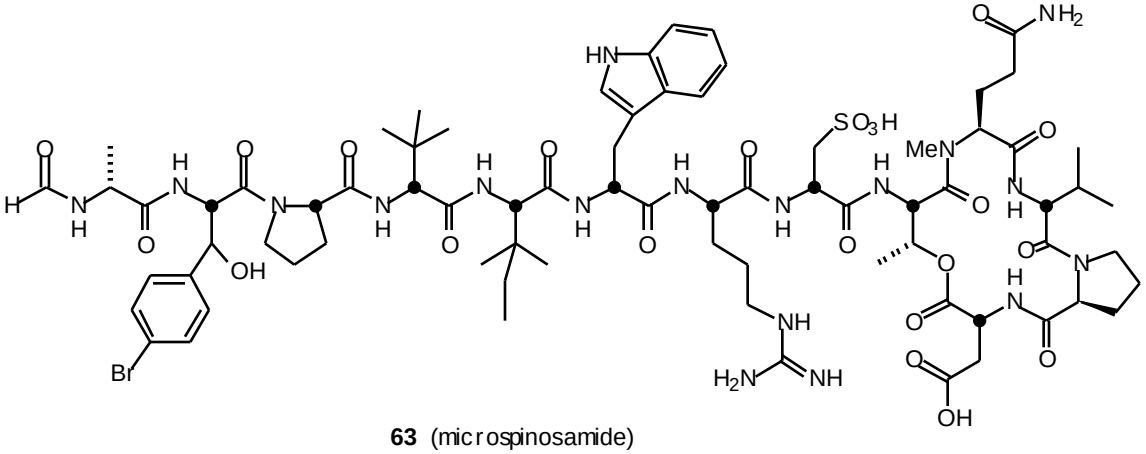


59 R = H (microginin 91-A)
60 R = Cl (microginin 91-B)



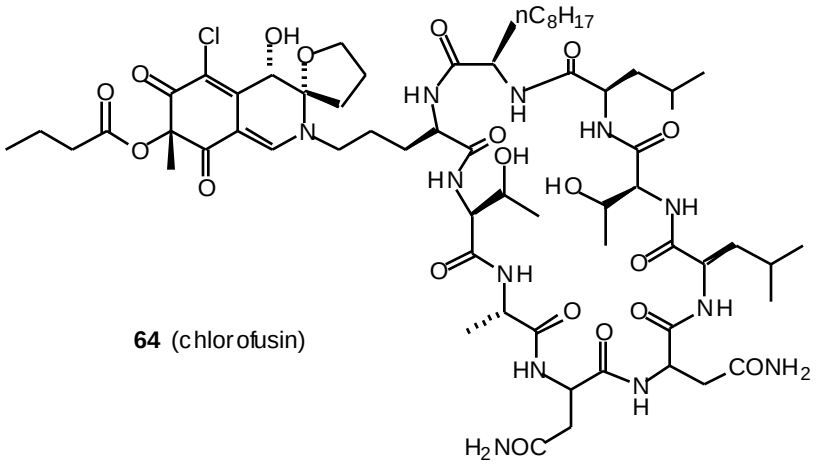
61 R = H (microginin 91-D)
62 R = Cl (microginin 91-E)

The novel cyclic depsipeptide microspinosamide (**63**), which incorporates thirteen amino acid residues, has been characterized from the sponge *Sidonops microspinosa* (32). This compound, which has the novel ß-hydroxy-*p*-bromophenylalanine residue, shows strong anti-HIV activity.



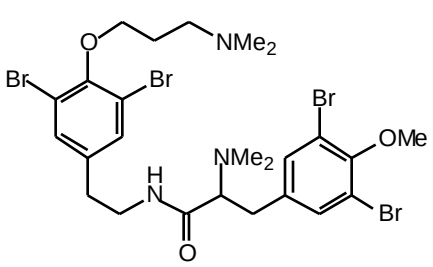
63 (microspinosamide)

A *Fusarium* sp. fungus has yielded the highly novel and complex chlorofusin (**64**), which is a p53-MDM2 antagonist (33).

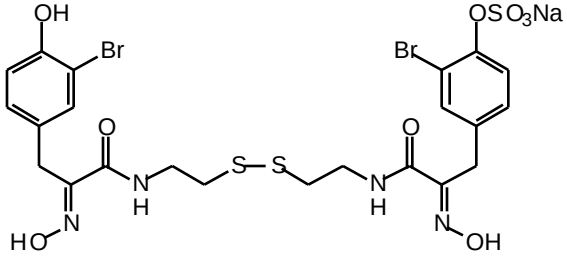


64 (chlorofusin)

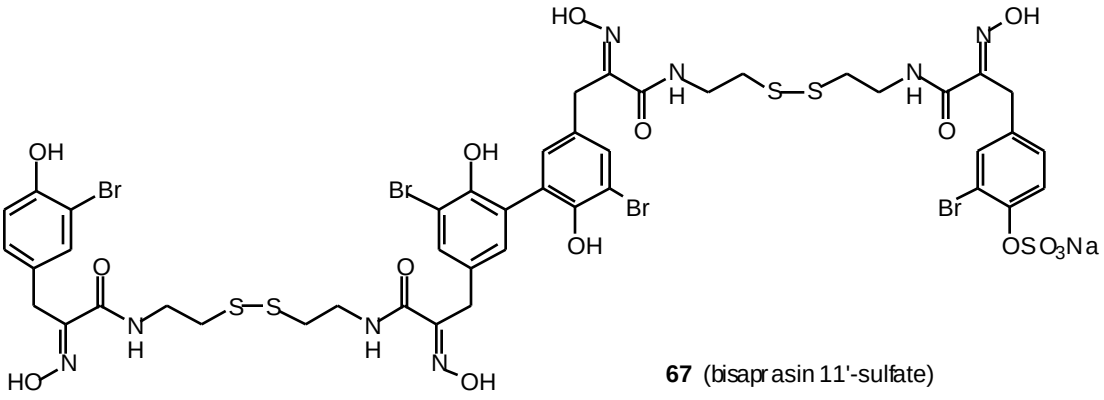
The number of new bromotyrosine derivatives that continue to be isolated from sponges seems to be infinite. The Indo-Pacific sponge *Aplysina* sp. has yielded aplyzanzine A (**65**) (34), and *Aplysinella rhax* contains psammaplin A 11'-sulfate (**66**) and bisaprasin 11'-sulfate (**67**) (35). Another study of this sponge identified **66** (as the *N*,*N*-dimethylguanidium salt) along with the new analogues **68**-**70** (36).



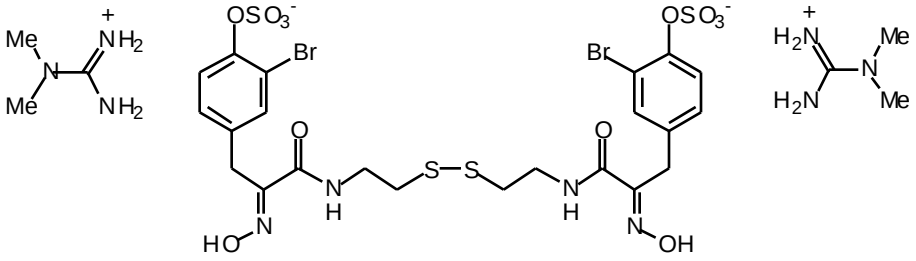
65 (aplyzanzine A)



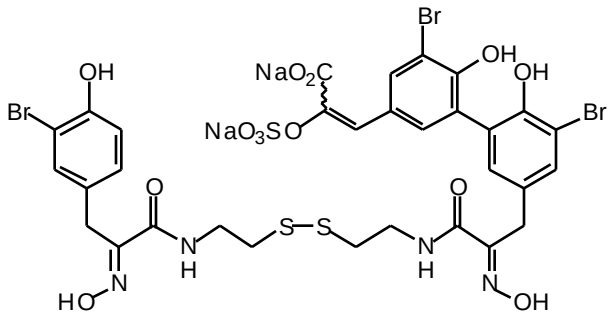
66 (psammaplin A11'-sulfate)



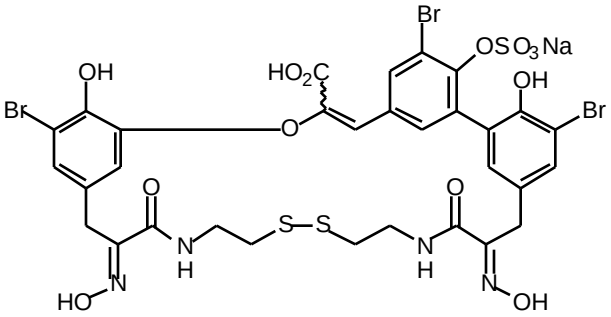
67 (bisaprasin 11'-sulfate)



68 (psammaplin A $_2$)

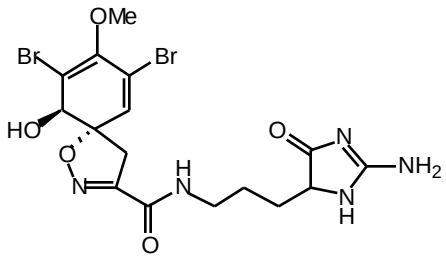


69 (aplysinellin A)

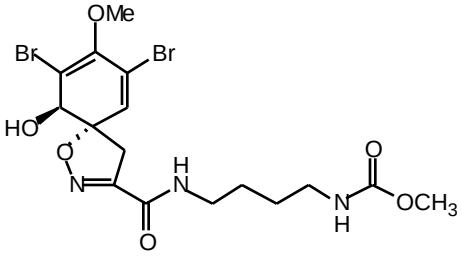


70 (aplysinellin B)

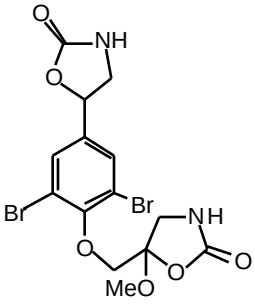
Several new transformed bromotyrosine (bromoisoxazolines) sponge metabolites have been identified. The Caribbean *Aplysina insularis* contains at least fourteen such compounds, one of which, 14-oxoaerophobin-2 (**71**) is a new metabolite (37). An earlier study of this sponge revealed the new metabolites **72** and **73** (38). The Australian marine sponge *Ianthella* sp. has afforded the novel ianthesines A-D (**74**-**77**) (39). Another Australian sponge, *Oceanapia* sp., has been found to contain **78** and **79**, which are the first examples of inhibitors of the mycobacterial enzyme mycothiol *S*-conjugate amidase (40). A new stereoisomer of fistularin-3, 1-*epi*-fistularin-3 (**80**), has been found in the sponge *Verongia aerophoba* collected in the Aegean Sea (41).



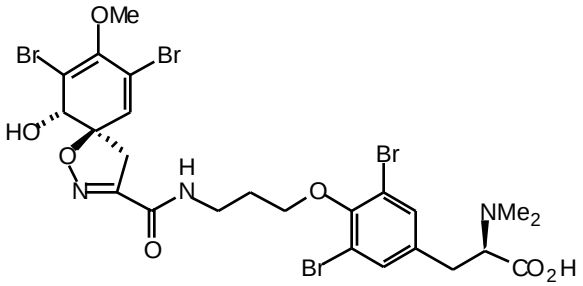
71 (14-oxoaerophobin-2)



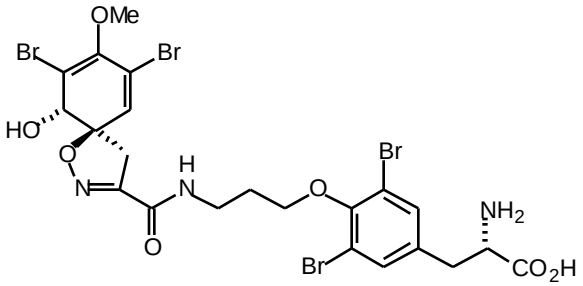
72



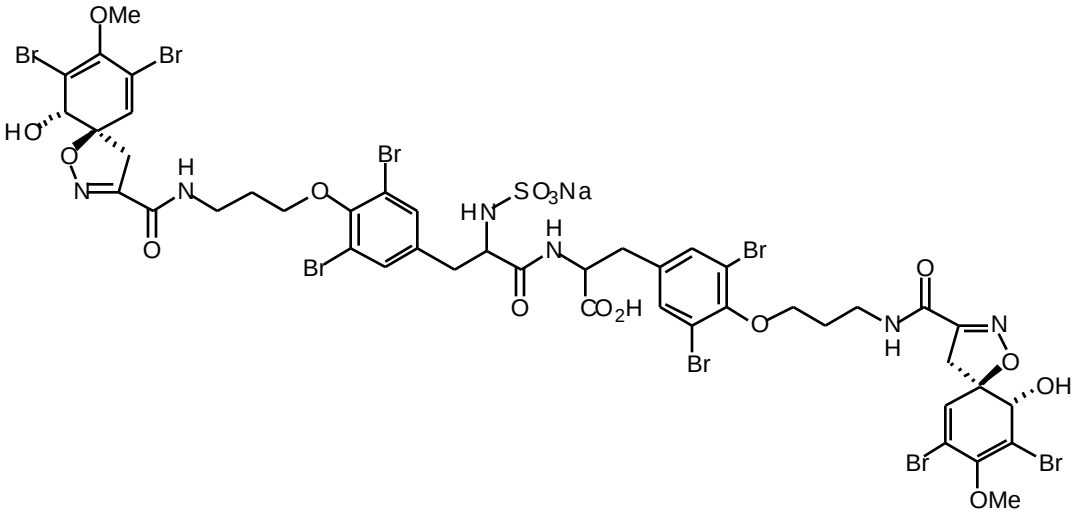
73



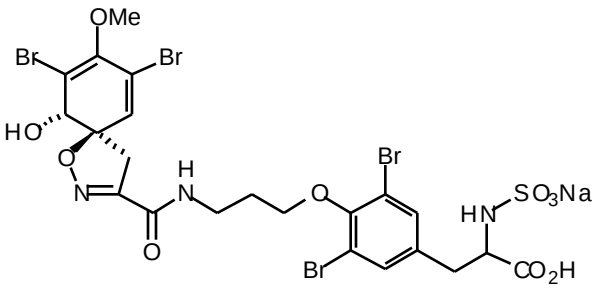
74 (ianthesine A)



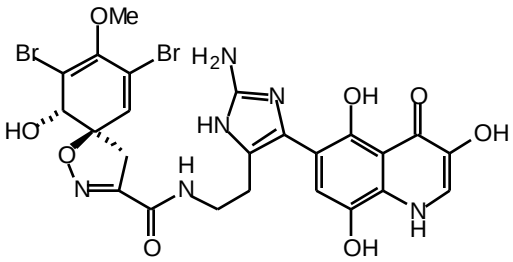
75 (ianthesine B)



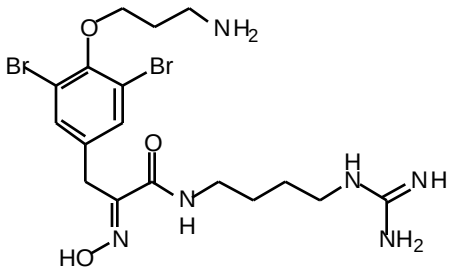
76 (ianthesine C)



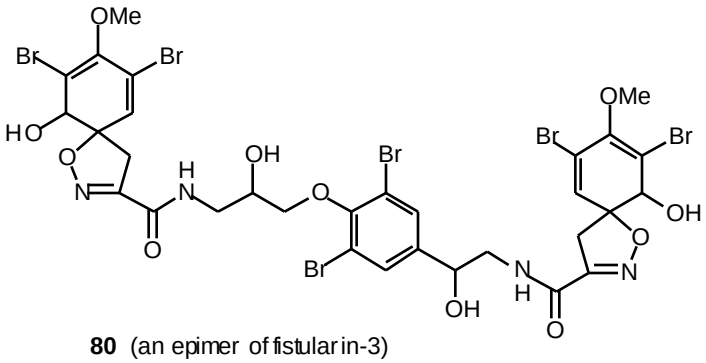
77 (ianthesine D)



78

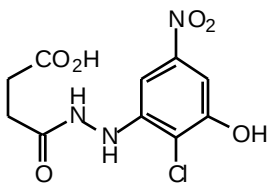


79

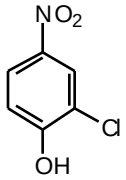


80 (an epimer of fistularin-3)

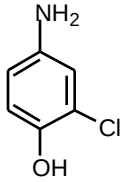
The carrot truffle, *Stephanospora caroticolor,* has been found to contain the novel nitrophenols stephanosporin (**81**) and 2-chloro-4-nitrophenol (**82**) (42). The latter compound is a commercial fungicide and the structure of **81** was confirmed by synthesis and is shown to be a biosynthetic precursor to **82**. This study also found 4-amino-2-chlorophenol (**83**). The sponge *Didiscus* sp. has yielded 2,5-dibromo-2-methoxybenzoic acid (**84**) (43) and the red alga *Symphyocladia latiuscula* contains the unusual cyclohexanonyl bromophenol symphyoketone (**85**) (44). This latter compound is a potent radical scavenger, twice as active as ascorbic acid. The known 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol is also present in this seaweed.



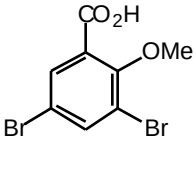
81 (stephanosporin)



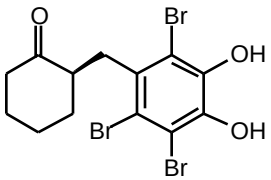
82



83



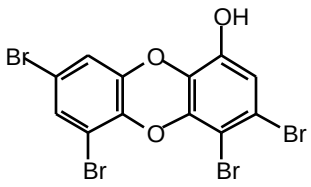
84



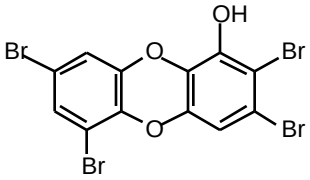
85 (symphyoketone)

An indisputable highlight of this *Updates* is the report of two brominated dioxins, **86** and **C**, in the Australian marine sponge *Dysidea dendyi* (45). The only other report of such compounds occurring in marine organisms, e.g., **C**, is in a Ph.D. thesis (46). The present work clearly represents a landmark discovery in dioxin science in being the first evidence of dioxins produced

by marine organisms. Presumably the abundant brominated diphenyl ethers are the precursors of **86** and **C**.

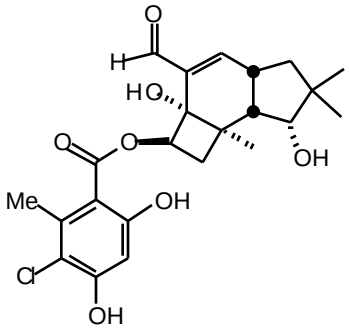


86

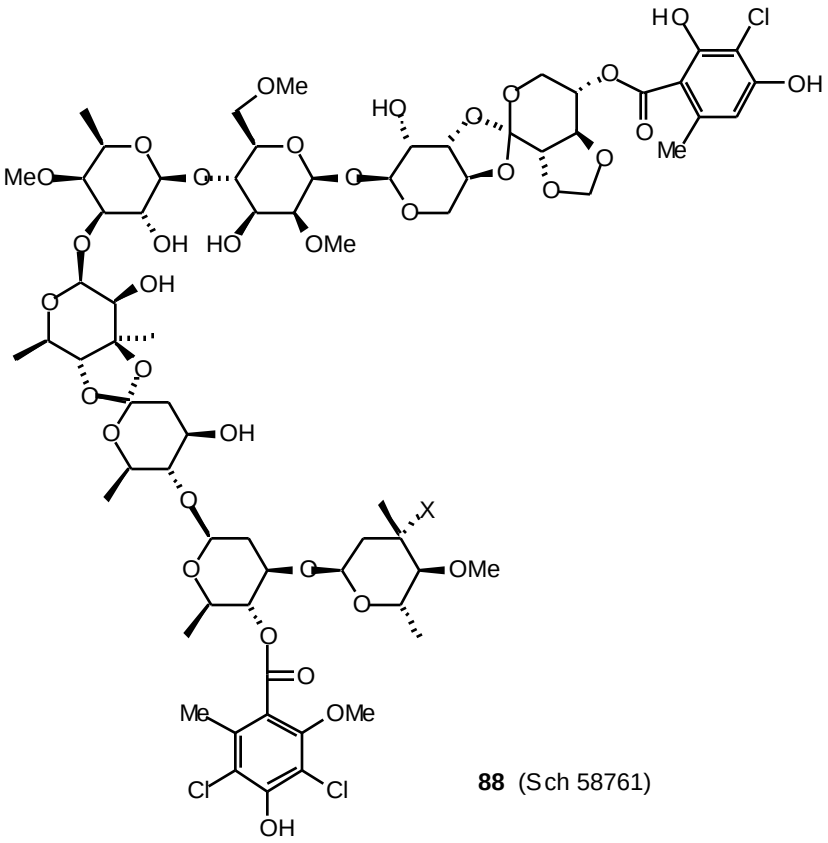


C

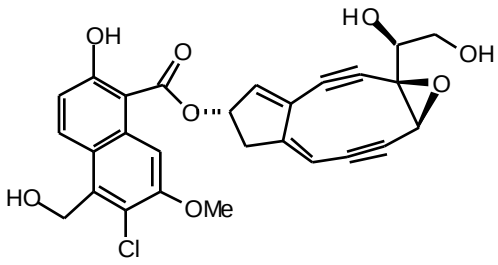
The pathogenic fungus *Armillaria novae-zelandiae* has yielded a new sesquiterpene chlorophenol, 6'-chloro-10α-hydroxymelleolide (**87**) (47). A new everninomicin antibiotic Sch58761 (**88**) was isolated from the fermentation broth of *Micromonospora carbonaceae* (48). This oligosaccharide chlorinated diphenol is a chloro derivative of ziracin (*Updates #9*). Based on synthetic studies, the structure of the previously isolated N1999-A2 (**D**) has been proposed as shown (49).



87 (6'-chloro-10α-hydroxymelleolide)



88 (Sch 58761)



D (N1999-A2)

III. Biohalogenation

Continued studies by Heinecke and co-workers (50) of the byproducts of peroxidase activity of white blood cells have shown that the generation of brominated pyrimidines by eosinophils and plasma bromide (20-200 μM) "might constitute a mechanism for cytotoxicity and mutagenesis at sites of inflammation." Thus, the eosinophil peroxidase-hydrogen peroxide system can generate 5-bromodeoxycytidine at plasma levels of bromide via either hypobromous acid or bromamines. Further conversion to 5-bromouracil and incorporation into DNA is observed. However, these brominated nucleic acid bases have not yet been detected *in vivo*.

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