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# The diversity of natural organochlorines in living organisms

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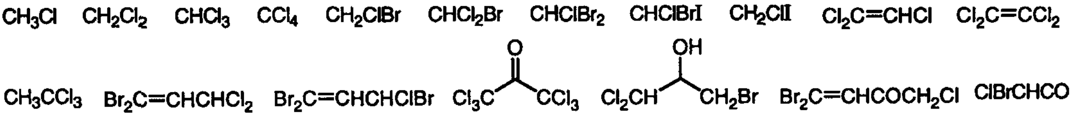
*Abstract:* Of the more than 2600 known naturally occurring organohalogen compounds, more than 1500 contain chlorine. These organochlorines, which range in structural intricacy from the ubiquitous fungal and plant metabolite chloromethane to the complex life-saving antibiotic vancomycin, are produced by marine and terrestrial plants, bacteria, fungi, lichens, insects, marine animals (sponges, sea hares, nudibranchs, gorgonians, tunicates), some higher animals, and a few mammals. New examples are continually being discovered and the total number of natural organohalogens may surpass 3000 by the turn of the century.

## INTRODUCTION

Forty years ago, the few known naturally occurring organochlorine compounds were considered chemical freaks, not to be taken seriously [1]. In 1968, Fowden wrote: 'present information suggests that organic compounds containing covalently bound halogens are found only infrequently in living organisms' [2]. However, in the past few years, the number of natural organochlorine compounds has grown to more than 1500, most of which are produced by living organisms, such as marine and terrestrial plants, bacteria, fungi, lichen, insects, marine animals, and some mammals. This extraordinary explosion of information was the subject of the first 'International Conference on Naturally Produced Organohalogens' in The Netherlands in 1993, and a comprehensive review of the 2500 known natural organohalogen compounds has recently appeared [3]. Earlier reviews on various aspects of this field are also available [4–16]. The present survey attempts to highlight the fantastic diversity of organochlorine chemicals in living organisms.

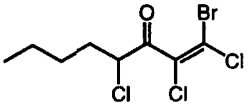
## SIMPLE ORGANOCHLORINES

A vast array of simple chlorinated alkanes and other small organochlorine compounds is known to be produced by living organisms, especially marine algae. A summary of these compounds is shown in Scheme 1. For example, chloromethane, which is also produced from natural combustion sources, is found in many species of wood-rotting fungi [17], marine algae [18], phytoplankton [19], giant kelp [20], the ice plant [18], some evergreen trees [21], mushrooms [22], potato tubers [23], and a bryozoan [24]. In wood-rotting fungi, chloromethane serves as a methyl donor for the biosynthesis of esters and anisoles such as veratryl alcohol, which plays a key role in the degradation of wood lignin [25]. It is noteworthy that both tri- and perchloroethylene are produced by several species of algae [26]. Nearly 40 organochlorine compounds have been isolated from the edible Hawaiian red seaweed *Asparagopsis taxiformis* [27,28], and some of these are shown in Scheme 1. Indeed, nearly 100 organohalogen compounds of all types have been characterized in this alga, which is prized for its flavor and aroma by native Hawaiians.



**Scheme 1** Simple organochlorines produced by living systems [3].

Some additional simple organochlorines include the octenone **1** from the red alga *Bonnemaisonia asparagoides* [29], dichloroacetamide (**2**) from *Marginisporum aberrans* [30], and the vinyl chloride **3** from blue-green alga [31]. Neocarzillin A (**4**), which is highly cytotoxic to K562 leukemia cells, is produced by *Streptomyces carzinostaticus* [32]. Caldariomycin (**5**), from the fungus *Caldariomyces fumago*, was one of the first naturally occurring organochlorine compounds to be discovered [33]. The novel calmodulin inhibitors KS-504a (**6**) and related cyclopentanes have been isolated from the fungus *Mollisia ventosa* and contain up to 69% chlorine by weight [34].



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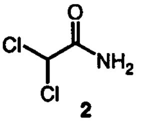

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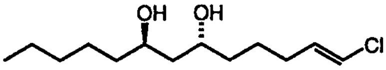

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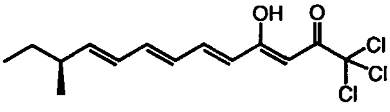

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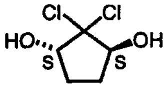

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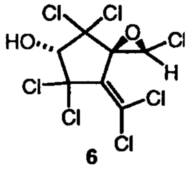

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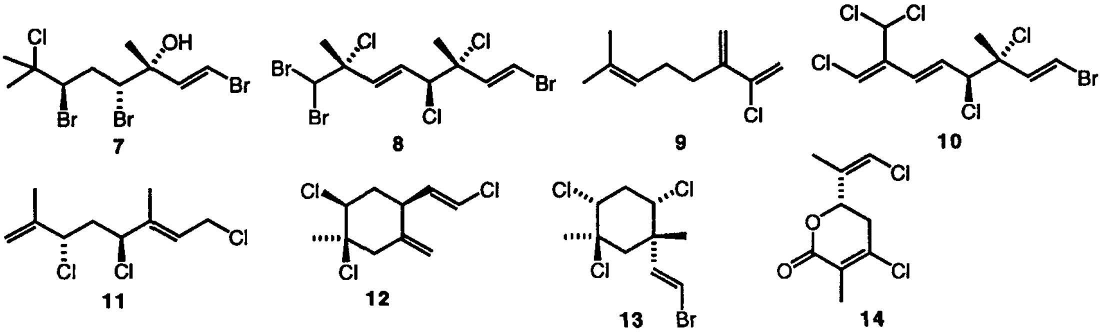
## TERPENES

### Monoterpenes

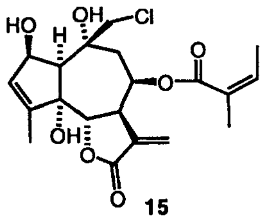
The first report of a chlorine-containing natural monoterpene appeared in 1973, which described the isolation of **7** and **8** from the sea hare *Aplysia californica* [35]. These compounds are probably derived from the animal's diet of alga [36]. Numerous other chlorinated monoterpenes have been identified in marine organisms and a small sampling is shown in Scheme 2. Several of these compounds, including telfairine (**13**), have potent insecticidal activity [37].



**Scheme 2** Chlorinated monterpenes from marine organisms [3].

### Sesquiterpenes

Myriad chlorine-containing terrestrial sesquiterpenes have been discovered, particularly possessing the guaianolide skeleton. Eupachlorin (**15**) from *Eupatorium rotundifolium* was one of the first such compounds to be isolated [38] and the new melampolide **16** was recently found in the plant *Enhydra fluctuans* [39]. Asian bracken ferns contain several chlorinated pterosins, such as pterosin F (**17**), which are respon-



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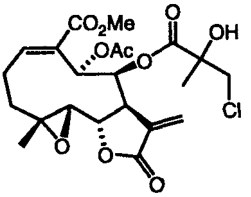

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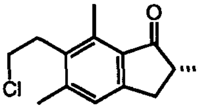

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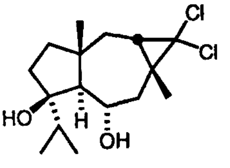

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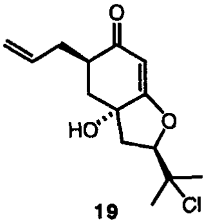
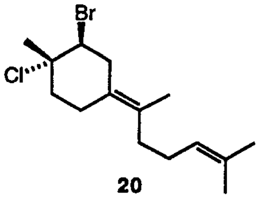


**19**

sible for cattle poisoning [40]. The interesting jaeschkenol (**18**) is found in the Himalayan plant *Ferula jaeschkeana* [41], and 12-chloroillifunone C (**19**) was isolated from *Illicium tashiroi* [42].

Marine organisms also produce many chlorinated sesquiterpenes, and some notable examples are preintricatol (**20**) from *Laurencia* red algae [43], the novel carbonimide **21** from the sponge *Pseudaxinyssa pitys* [44], and the norsesquiterpene napalilactone (**22**), from the soft coral *Lemnalia africana* [45]. Numerous chlorinated chamigrenes, such as intricatene (**23**) from *Laurencia intricata* [46], are known.



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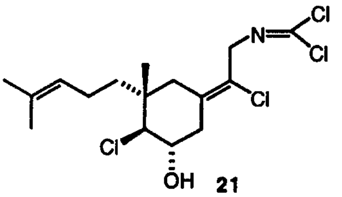

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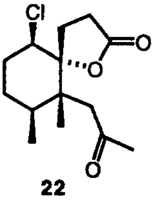

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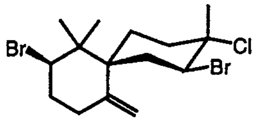

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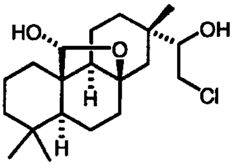
## Diterpenes

Although most chlorine-containing diterpenes are marine-derived, a few terrestrial examples are known. A recent example is **24** from the Brazilian plant *Vellozia bicolor* [47]. Interestingly, the corresponding epoxide is not converted to **24** under the isolation conditions. The sea hare *Aplysia dactylomela* produces dactylomelol (**25**) [48], and the sponge *Acanthella* spp. has been a rich source of diterpene isonitriles such as kalihinol A (**26**) [49]. The New Caledonian ascidian *Lissoclinum voeltzkowi* produces the cytotoxic labdane derivative **27** [50].



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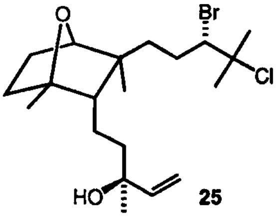

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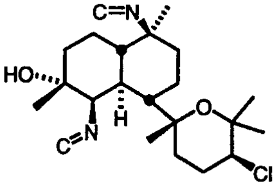

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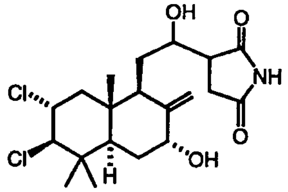

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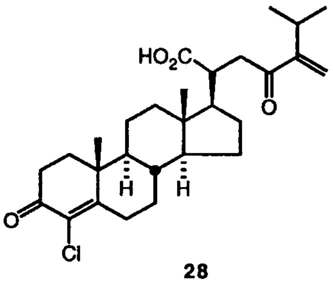
## STEROIDS

Several examples of terrestrial plant chlorine-containing steroids are known, but the most interesting are the Maui sponge metabolites such as kiheisterone C (**28**) [51] and the German cockroach pheromones such as blattellastanoside A (**29**) [52].



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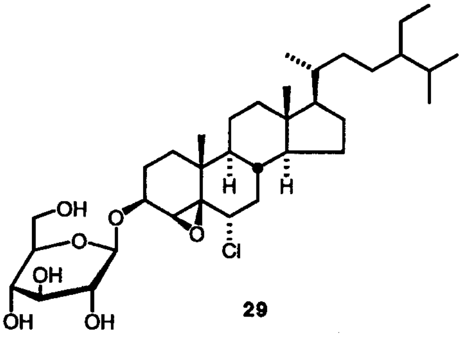
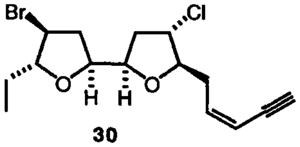


**29**

## MARINE ACETOGENINS

A very large number of halogenated marine nonterpenoid C15 acetogenins are known, particularly from *Laurencia* red algae [3]. For example, notoryne (**30**) is produced by the Japanese red alga *Laurencia nipponica* [53] and intricenyne (**31**) is found in *L. intricata* [54]. The Guam 'bubble shell' (*Haminoea cymbalum*) contains kumepaloxane (**32**), a feeding deterrent against carnivorous fishes [55]. The Italian sea hare *Aplysia punctata* produces the novel bicyclic ether **33** [56].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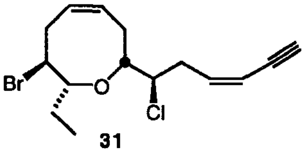
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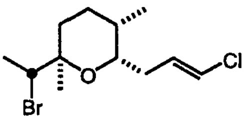
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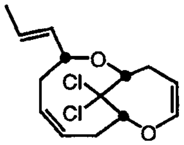
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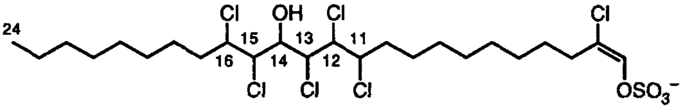
## FATTY ACIDS

Numerous chlorinated fatty acids are known from fungi and phytoflagellates, some of which contain six chlorine atoms. For example, malhamensilipin A (**34**) is found in the chrysophyte *Poterioochromonas malhamensis* [57]. The blue-green alga *Lyngbya majuscula* has been a rich source of novel fatty acid derived amides such as malyngamide A (**35**) [58].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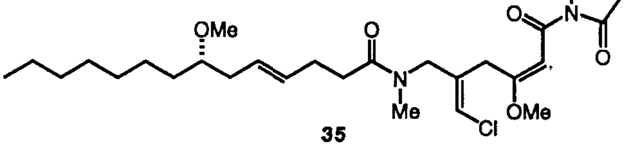
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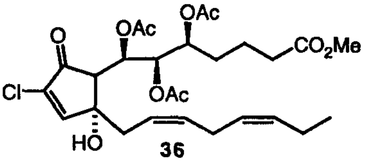
## PROSTAGLANDINS

Nearly 30 chlorine-containing prostaglandins have now been isolated from several marine animals. These compounds possess pronounced anticancer activity. For example, the octocoral *Telesto riisei* produces punaglandin 1 (**36**) [59] and the brown alga *Egregia menziesii* has yielded egregiachloride A (**37**) [60].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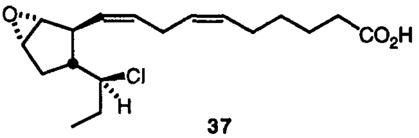
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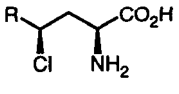
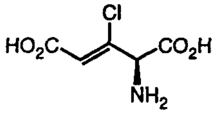
## AMINO ACIDS AND PEPTIDES

Several simple amino acids and peptides have been found in microorganisms such as *Streptomyces* and *Pseudomonas* [3]. Some are shown here (**38**–**43**). Although not an amino acid, the related chloramphenicol (**44**) has been a commercial antibiotic for many years and is produced by *Streptomyces venezuelae* [61] and the moon snail (*Lunatia heros*) [62].


**38** R = Cl
**39** R = $CH_3$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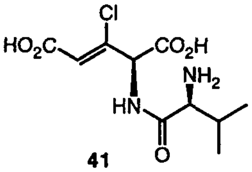
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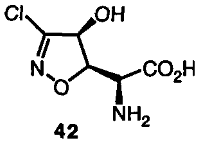
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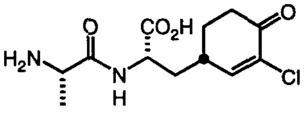
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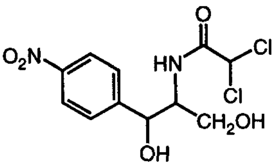
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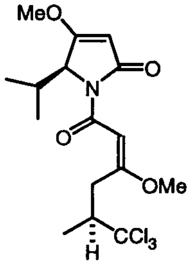
The marine sponge *Dysidea herbacea* has proven to be a rich source of novel amino acid and peptide-derived metabolites such as dysidin (**45**) [63] and dysidenin (**46**) [64]. These trichloromethyl compounds may be a source of chloroform in the oceans. Several large peptides, both acyclic and cyclic, contain chlorine. Islanditoxin, which was isolated in 1955 from a culture of *Penicillium islandicum*, contains two chlorines on a proline residue [65], and cryptophycin A (**47**) is one of many related *Nostoc* sp. blue-green algae metabolites with excellent anticancer activity against solid tumors [66]. The cardioactive cyclic peptide puwainaphycin C, which is produced by the blue-green alga *Anabaena* sp., contains the unprecedented amino acid 3-amino-14-chloro-2-hydroxy-4-methylpalmitic acid [67]. The *threo*-4-chlorothreonine residue is found in several *Pseudomonas syringae* cyclic peptides [68]. The fungal pathogen *Periconia circinata* produces several interesting chlorine-containing peptides such as peritoxin A (**48**) [69].



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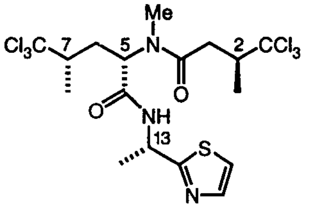

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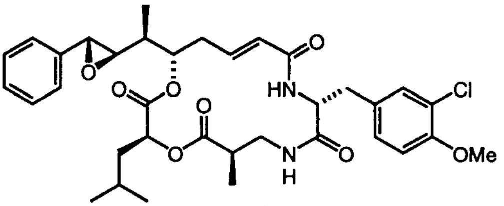

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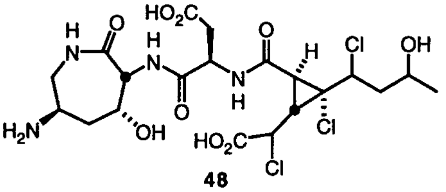

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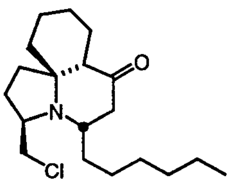
## ALKALOIDS

Despite the enormous number of known terrestrial plant alkaloids, only a few chlorine-containing examples have been discovered. Some early examples include jaconine (*Senecio jacobaea*) [70], doronine (*Doronicum macrophyllum*) [71], lolidine (*Lolium cuneatum*) [72], and acutumine (*Sinomenium acutum*) [73]. The Tasmanian ascidian *Clavelina cylindrica* produces the novel alkaloids cylindricine A (**49**) and B [74]. The Asian folk medicine plant *Houttuyniae cordata* has yielded 7-chloro-6-demethylcepharadione B (**50**) [75], and epibatidine (**51**), which is a potent analgesic, is secreted by the Ecuadorian frog *Epipedobates tricolor* [76].



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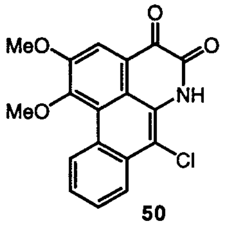

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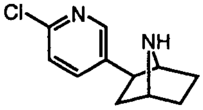

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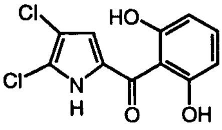
## HETEROCYCLES

### Pyrroles

The high reactivity of pyrroles towards electrophiles portends the large number of naturally occurring halogenated pyrroles. Several chlorinated pyrroles are produced by *Pseudomonas* spp., such as pyoluteorin (**52**) [77] and pyrrolnitrin (**53**) [78], and the optically active neopyrrolomycin (**54**) is found in cultures of a *Streptomyces* sp. [79]. The fungus *Auxarthron umbrinum* produces rumbrin (**55**), which may be useful in the treatment of ischemia [80]. The sponge *Phorbas aff. clathrata* contains four chlorinated phorbazoles (e.g., **56**) [81], and a set of novel pyralomicins, such as **57**, is produced by *Actinomadura spiralis* [82].



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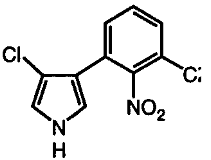

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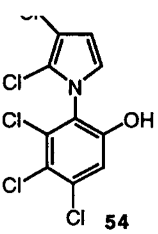

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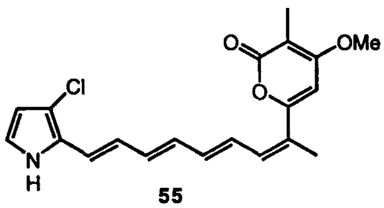

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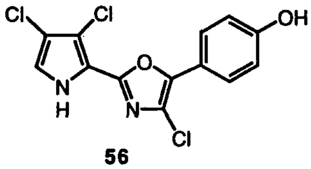

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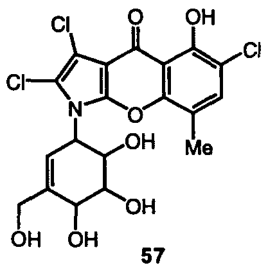
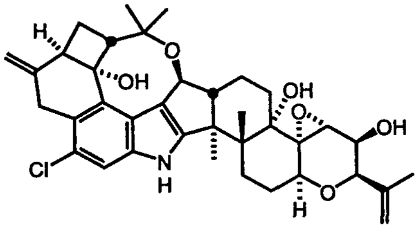


**57**

## Indoles

Chlorinated indoles are widespread in living systems. Indeed, the simple 3-chloroindole is found in the acorn worm *Ptychodera flava laysanica* [83], and the New Zealand red alga *Rhodophyllis membranacea* produces eight novel chlorinated indoles including 2,3-dichloro-7-bromoindole [84]. Several terrestrial plants (green peas, fava bean, grasspea, sweet pea, lentil, vetch) produce 4-chloroindole-3-acetic acid and the methyl ester as growth hormones [85]. The fava bean also contains 4-chloro-6-methoxyindole which is thought to be the precursor of a potent mutagen that forms during intragastric nitrosation [86]. The blue-green alga *Hapalosiphon fontinalis* is the source of a dozen chlorinated isonitriles [87], and related compounds are produced by *Fischerella* spp. blue-green algae [88]. The deep water Bahamas sponge *Batzella* sp. is the source of several chlorine-containing indoles, and the fungus *Penicillium crustosum* produces three 6-chloroindole penitrem metabolites of almost incredible molecular complexity (e.g., penitrem A (**58**)) [89]. The bryozoan *Chartella papyracea* has yielded the stunningly complex chartelline A (**59**) and several related halogenated indoles [90]. In contrast, the bryozoan *Amathia convoluta* contains the simple convolutamydine B (**60**) [91]. More recently, the bryozoan *Securiflustra securifrons* has been found to contain four chlorinated securamines, e.g., **61** [92].



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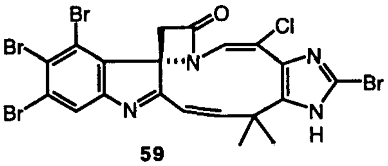

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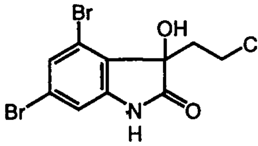

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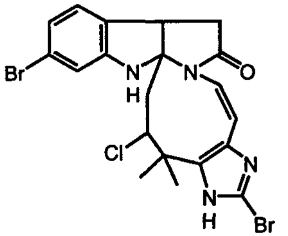
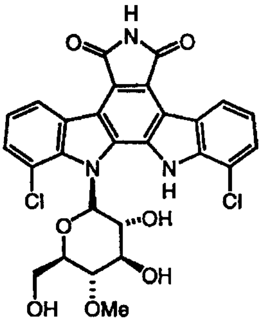


**61**

Other notable chlorine-containing indole natural products include the 8-chlororugulovasines from *Penicillium islandicum* [93], the pyrindamycins (duocarmycins) from *Streptomyces* spp. [94], and the sporidesmins from *Sporidesmium bakeri* and *Pithomyces chartarum*, fungi that cause facial eczema in farm animals [95].

## Carbazoles and related heterocycles

The simple chlorine-containing carbazoles chlorohyellazole and 3-chlorocarbazole are found in a blue-green alga (*Hyella caespitosa*) [96] and bovine urine [97], respectively. The more complex rebeccamycin (**62**) [98] is the prototype of a growing number of natural chlorinated indolocarbazoles. For example, the blue-green alga *Tolypothrix tjipanasensis* produces 13 chlorinated indolo[2,3-*a*]carbazoles, such as tjiipanazole A1 (**63**) [99]. The Kauaian terrestrial blue-green alga *Dichothrix baueriana* has yielded three chlorinated β-carbolines (e.g., bauerine B (**64**)), which are active against *Herpes* simplex virus [100].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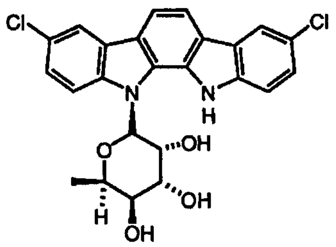
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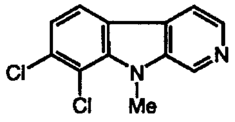
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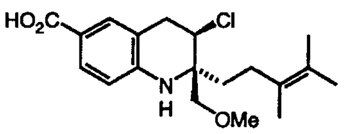
## Other nitrogen heterocycles

Numerous other chlorinated nitrogen heterocycles are known from living systems. Thus, the antibiotic virantmycin (**65**) is produced by *Streptomyces nitrosporeus* [101] and young corn roots (*Zea mays*) have afforded the chlorinated benzoxazinone **66** [102]. The antifungal chlorophenazine **67** has been isolated from *Streptosporangium* sp. [103].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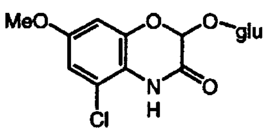
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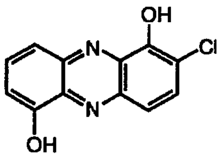
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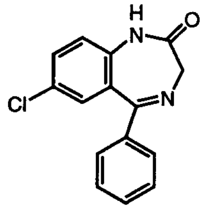
Surprisingly, seven chlorine-containing benzodiazenes, such as **68**, are found in wheat and potato tubers [104]. Several nucleic acid bases contain chlorine, such as **69** from *Streptomyces rishiriensis* [105], and kumusine (**70**) from a *Theonella* sp. sponge [106] and the sponge *Trachycladus laevispirulifer* [107].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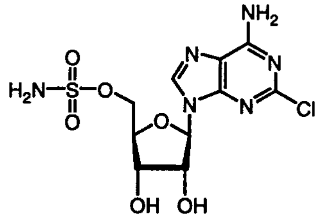
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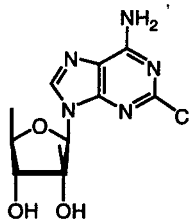
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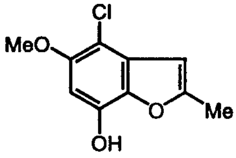
## Oxygen heterocycles

Several chlorine-containing oxygen heterocycles are known and from a variety of sources. The fungus *Phialophora asteris* produces furasterin (**71**) [108] and chloromycorrhizinol A (**72**) is found in the roots of *Monotropa hypopitys* [109]. The ubiquitous fungal toxin ochratoxin A (**73**) has been isolated from several fungi [110] and the flavone sordidone (**74**) is found in several *Lecanora* spp. lichens [111]. The psoralen saxalin (**75**) is found in several plants including parsley [112].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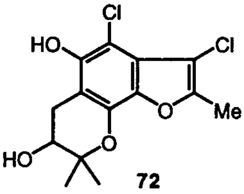
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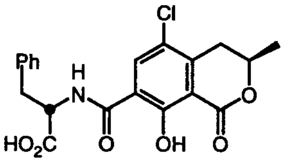
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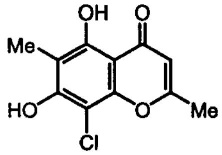
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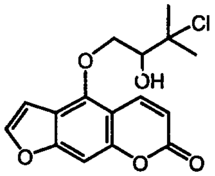
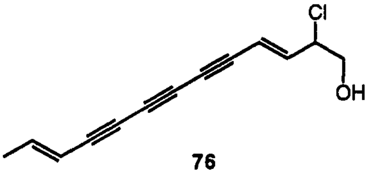

**75**

## POLYACETYLENES

A very large number of polyacetylenes and biochemically derived thiophenes are present in terrestrial plants and more than 30 contain chlorine [113], two of which are shown (**76**, **77**). The nudibranch *Diaulula sandiegensis* secretes nine chloroacetylenes as chemical defensive agents. The most abundant is **78** [114].



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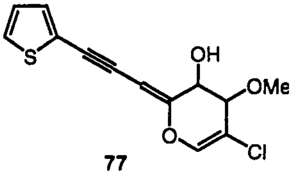

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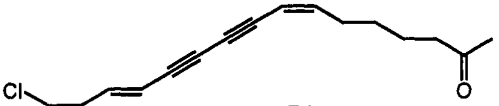


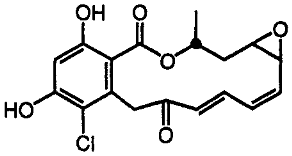
**78**

## ENEDIYNES

The remarkable and growing group of enediyne natural products contain chlorine in a few cases. Thus, kedarcidin and C-1027, both of which are potent anticancer agents from soil microbes, are chlorinated [115,116]. Kedarcidin is a 2-chloropyridine derivative and C-1027 contains a chlorophenol ring.

## MACROLIDES

Several chlorine-containing macrolides are known. Chlorothricin and its derivatives are produced by *Streptomyces* spp. [117] and the well-known maytansinoids are found in numerous microorganisms [118,119]. The simpler monorden (radicidol) (**79**) is produced by *Monosporium bonorden* [120] and *Nectria radicicola* [121], and the related 6-chlorodehydrocurvularin (**80**) was extracted from the fungus *Cochliobolus spicifer* [122].



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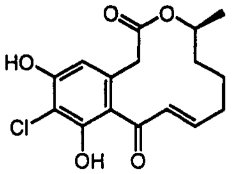
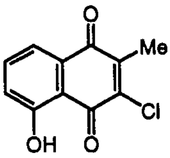


**80**

A collection of remarkably active antitumor sponge metabolites, the spongistatins, have been discovered in *Spirastrella spinispirulifera*, some of which contain the chlorovinyl moiety [123].

## QUINONES



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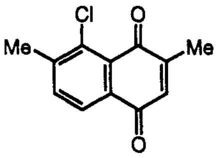

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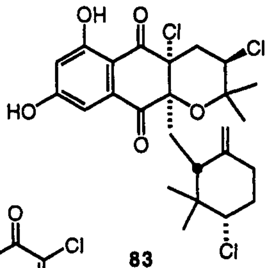

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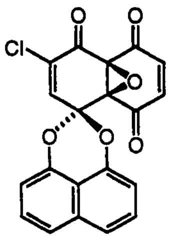

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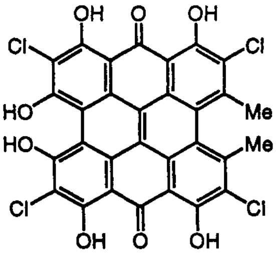

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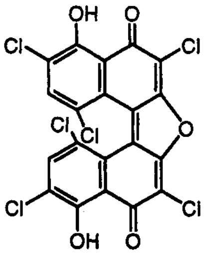
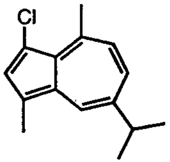


**86**

Many aromatic quinones of varying complexity contain chlorine. The simple **81** is found in several fungi [124] and 8-chlorochimaphilin (**82**), which has antibiotic activity, was recently isolated from *Moneses uniflora* [125]. A series of eight chlorinated napyradiomycins (e.g., **83**) have been isolated from *Chainia rubra* [126] and four extraordinary chloropalmarumycins (e.g., **84**) were found in the West Borneo forest soil microbe *Coniothyrium* sp. [127]. The novel quinone **85** is produced by the lichen *Nephroma laevigatum* [128], and the unusual ring system embodied in the purple pigment **86** has been discovered in a soil fungus [129]. The venerable tetracycline antibiotics include at least ten chlorine-containing examples (e.g., aureomycin) [130]. These quinone derivatives are produced by several *Streptomyces* spp.

## AROMATIC COMPOUNDS

Although most of the known chlorinated aromatic compounds are phenolic, a few are simple aromatic derivatives. For example, 1,2,3,4-tetrachlorobenzene is a major component of needlerush oil (*Juncus roemerianus*) [131] and a deep sea gorgonian has yielded azulene **87** [132]. The novel nostocyclophanes (e.g., **88**) are produced by the blue-green alga *Nostoc linckia* [133], and 3-chloroanthranilic acid is found in cultures of *Pseudomonas aureofaciens* [134].



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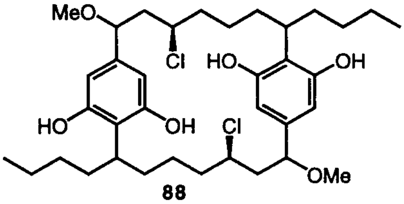
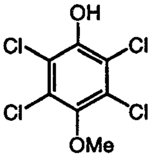


**88**

## PHENOLS

Like pyrroles, the great reactivity of phenols in electrophilic substitution reactions has allowed nature to produce an enormous array of natural chlorinated phenols, both simple and complex. A *Penicillium* sp. produces 2,4-dichlorophenol [135] and at least a dozen species of ticks biosynthesize 2,6-dichlorophenol as a sex pheromone [136]. Chloride labeling studies confirm the biosynthesis of this compound within the insect [137]. The earliest terrestrial natural chlorophenol to be isolated was drosophilin A (**89**) from *Drosophilia subatrata* [138], and the fungus *Fomes robiniae* contains the nitro derivative **90** [139]. Amudol (**91**) is found in *Penicillium martinsii* [140], and several other chlorine-containing benzyl alcohols and benzaldehydes are produced by white-rot and other fungi [141]. There is also mounting evidence that 2,4,6-trichlorophenol is a natural product of soil microbes [142]. The Florida acorn worm *Ptychodera bahamensis* contains four chlorophenols (e.g., **92**) [143], and **93** has been discovered in the blue-green alga *Anacystis marina* [144]. Some chlorinated tyrosines are found in the proteins of locusts [145] and molluscs [146], where they are believed to improve adhesion between protein fibers and sheets [146].



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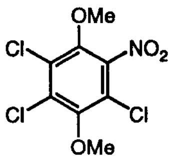

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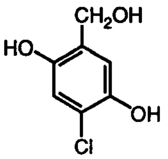

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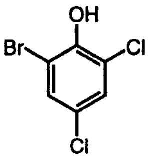

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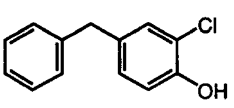
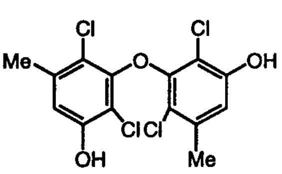


**93**

Several chlorine-containing diphenyl ethers have been reported, mainly from fungi and algae. The freshwater fungus *Kirschsteiniothelia* sp. produces **94** [147], and the terrestrial blue-green alga *Fischerella ambigua* has afforded ambigol A (**95**) [148]. This latter compound inhibits HIV reverse transcriptase. A number of chlorinated fucols have been extracted from the brown alga *Analipus japonicus* [149]. The toxic mushroom *Russula subnigricans* contains seven chlorinated russuphelins, such as russuphelol (**96**) [150].

Other natural chlorine-containing phenolic derivatives are known, but are too numerous to list here. These include transformed tyrosines from sponges, depsides and depsidones from lichens, and xanthones and anthraquinones from lichens and fungi. For a complete summary of these myriad organochlorine compounds, see ref. 3. Other examples are the antifungal agent griseofulvin (**97**) [151] and aspirochlorine (**98**) [152], both found in several fungi, and armillaridin (**99**) from *Armillaria mellea* [153].



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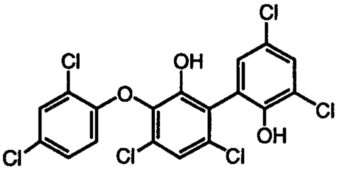

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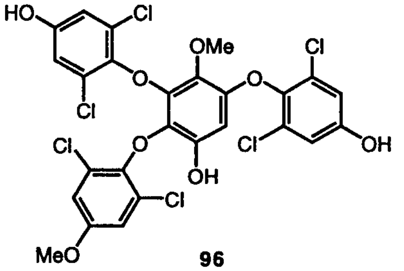

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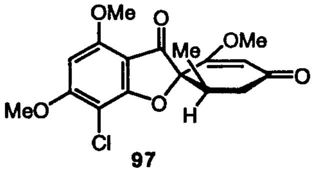

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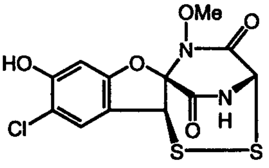

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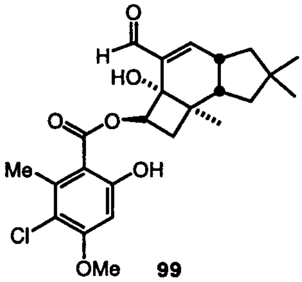
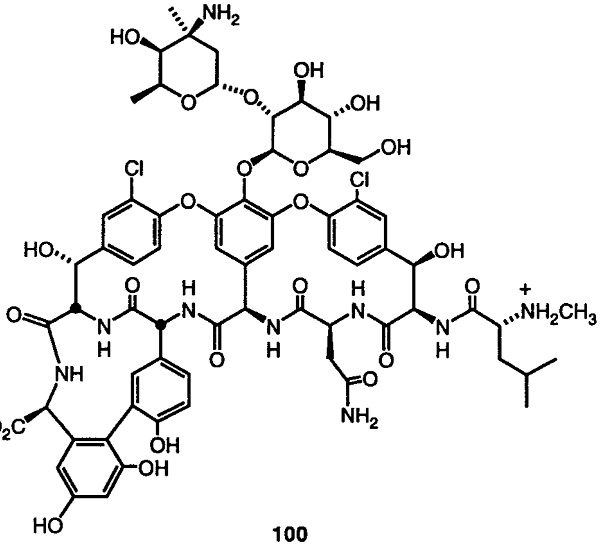


**99**

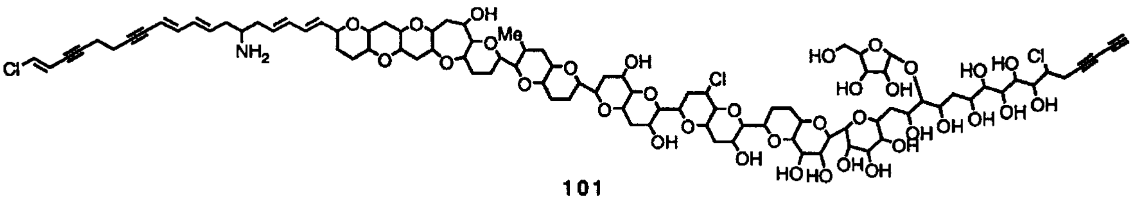
Perhaps the most medicinally important organochlorine compound is vancomycin (**100**), the glycopeptide antibiotic and the drug of choice to treat methicillin-resistant *Staphylococcus aureus* infections, particularly those that occur in hospitals [154]. Most of the 200 known glycopeptides contain chlorine [155].



**100**

## MISCELLANEOUS

A fitting conclusion is to mention the isolation of prymnesin-2 (**101**) from the red tide alga *Prymnesium parvum* [156]. This immense molecule, $C_{96}H_{136}Cl_3NO_{35}$, is a potent ichthyotoxin and the first red tide toxin found to contain chlorine.



**101**

## SUMMARY

The number of reported natural organochlorines from living organisms continues to increase, and these discoveries parallel our advances in collection, isolation, bioassay, and spectroscopic techniques. Since only a small percentage of living organisms have been examined for their chemical content, especially marine organisms, it is certain that a large number of new organochlorine compounds is awaiting discovery. For example, of the 4000 species of bryozoans, fewer than 1% have been studied in this regard.

Since mammals, including humans, utilize *in vivo* chlorination in white blood cells as part of the immune process, it is only a matter of time before organochlorine compounds are found to occur naturally in humans.

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