G.W. Gribble

# A Survey of Natural Organohalogen Compounds

## Abstract

New naturally occurring organohalogen compounds continue to be discovered. As of mid-1996 the number of such distinct compounds is 2,730, most of which contain chlorine or bromine. These organohalogens are produced by marine and terrestrial plants, bacteria, fungi, lichens, insects, marine animals, some higher animals, and a few mammals. The total number of natural organohalogens may surpass 3,000 by the turn of the century.

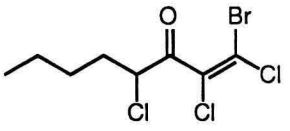
## Introduction

Forty years ago, the few known naturally occurring organohalogen compounds were considered aberrations. In 1968, Fowden wrote: 'present information suggests that organic compounds containing covalently bound halogens are found only infrequently in living organisms' (Fowden, 1968). Over the past decade, it has become clear that many organisms use halogen as a normal component of their biochemical processes and synthesize organo-halogens for survival. This extraordinary explosion of information was the subject of the first 'International Conference on Naturally Produced Organohalogens' in The Netherlands in 1993. A comprehensive review of all known natural organohalogen compounds has recently appeared (Gribble, 1996a). Earlier reviews on various aspects of this field are cited in this monograph. The present chapter attempts to highlight the fantastic diversity of organohalogen chemicals in living organisms and the remarkable synthetic virtuosity of nature. All references to organohalogens that are not explicitly cited herein are found in Gribble (1996a, 1996b).

## Simple Organohalogens

A vast array of simple halogenated alkanes and other low molecular weight organohalogen compounds is known to be produced by living organisms. For example, chloromethane, which is also produced from natural combustion sources, is found in many species of wood-rotting fungi, marine algae, phyto-

plankton, giant kelp, the ice plant, some evergreen trees, mushrooms, potato tubers, and a bryozoan. Both tri- and perchloroethylene are produced by 26 species of algae. Nearly 100 organohalogen compounds have been isolated from the edible Hawaiian red seaweed *Asparagopsis taxiformis*, which is prized for its flavor and aroma by native Hawaiians. Examples include the octenone **1** from the red alga *Bonnemaisonia asparagoides*, dichloroacetamide (**2**) from *Marginisporum aberrans*, and the vinyl chloride **3** from a blue-green alga. Neocarzillin A, (**4**) which is highly cytotoxic to K562 leukemia cells, is produced by *Streptomyces carzinostaticus* (Nozoe *et al.*, 1992). Caldariomycin (**5**), from the fungus *Caldariomyces fumago*, was one of the first naturally occurring organohalogen compounds to be discovered. 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.

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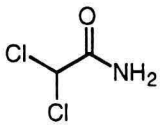


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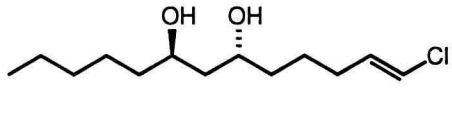


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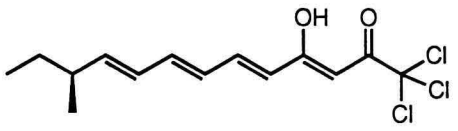


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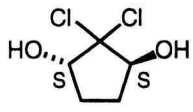


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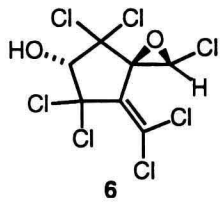


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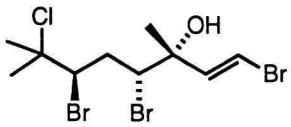
## Terpenes

The first report of a halogen-containing monoterpene appeared in 1973 with the isolation of **7** and **8** from the sea hare *Aplysia californica*. These compounds are probably derived from the animals' algae diet. Numerous other halogenated monoterpenes have been identified in marine organisms, and several of these compounds, for example telfairine, have potent insecticidal activity.

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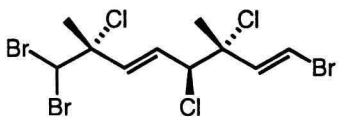


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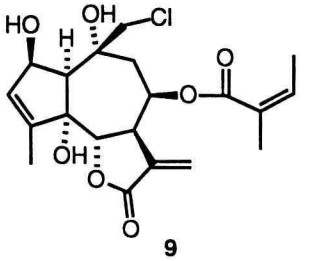
Myriad chlorine-containing terrestrial sesquiterpenes have been discovered, particularly possessing the guaianolide skeleton. Eupachlorin (**9**) from *Eupatorium rotundifolium* was one of the first such compounds to be isolated. Asian bracken ferns contain several chlorinated pterosins, such as pterosin F (**10**).

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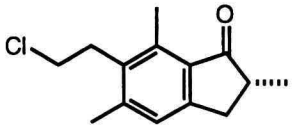
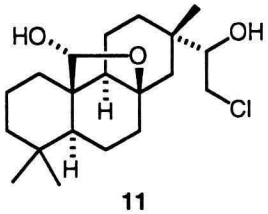



10

Although most halogen-containing diterpenes are marine-derived, a few terrestrial examples are known. A recent example is **11** from the Brazilian plant *Vellozia bicolor* (Pinto *et al.*, 1991). Interestingly, the corresponding epoxide is not converted to **11** under the isolation conditions. The sea hare *Aplysia dactylomela* produces dactylomelol (**12**), and the sponge *Acanthella* sp. has been a rich source of diterpene isonitriles such as kalihinol A (**13**).

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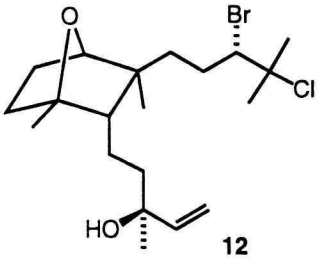


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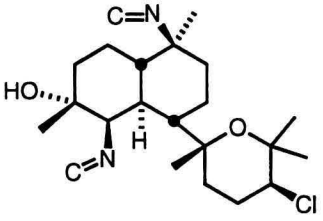


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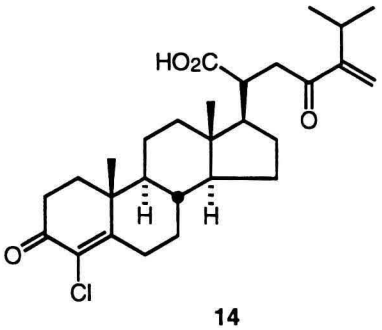
## Steroids

Several examples of terrestrial plant chlorine-containing steroids are known, but the most interesting are the Maui sponge metabolites such as kiheisterone C (**14**) (Carney *et al.*, 1993), and the German cockroach pheromones such as blattellastanoside A (**15**) (Sakuma and Fukami, 1991).

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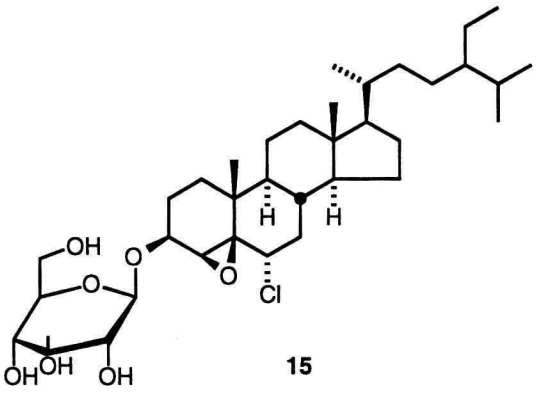


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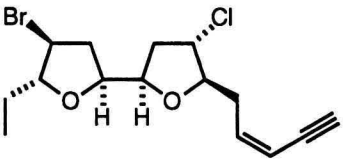
An extraordinary observation is the *in vitro* formation of three cholesterol chlorohydrins from cholesterol, chloride, hydrogen peroxide, and myeloperoxidase. Since myeloperoxidase is a component of human atherosclerotic lesions, cholesterol chlorohydrins might play a role in this disease (Heinecke *et al.*, 1994).

## Marine Acetogenins

A very large number of halogenated marine nonterpenoid C15 acetogenins are known, particularly from *Laurencia* red algae. For example, notoryne (**16**) is produced by the Japanese red alga *Laurencia nipponica* and intricenyne (**17**) is found in *L. intricata*. The Guam 'bubble shell' (*Haminoea cymbalum*) contains kumepaloxane (**18**), a feeding deterrent against carnivorous fishes.

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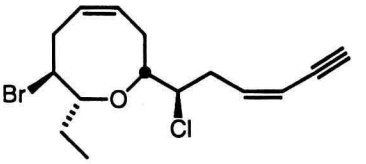


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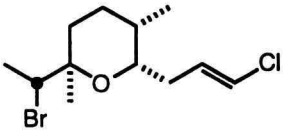
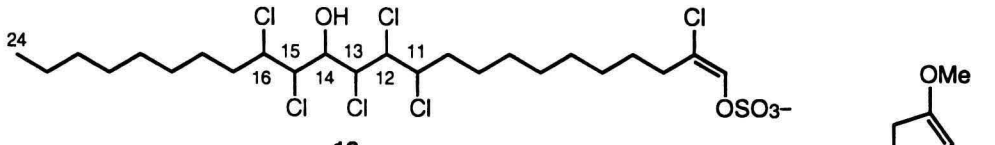



**18**

## Fatty Acids

Numerous chlorinated fatty acids are known from fungi and phytoflagellates, some of which contain six chlorine atoms. For example, malhamensilipin A (**19**) is found in the chrysophyte *Poterioochromonas malhamensis* (Chen *et al.*, 1994). The blue-green alga *Lyngbya majuscula* has been a rich source of novel fatty acid derived amides such as malyngamide A (**20**). The Okinawan sponge *Xestospongia* sp. contains 17 brominated fatty acids (Li *et al.*, 1995).

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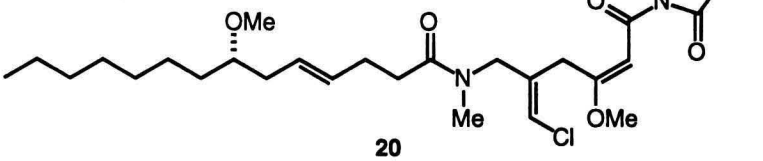
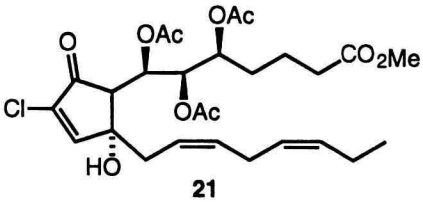



**20**

## 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 (**21**) and the brown alga *Egregia menziesii* has yielded egregiachloride A (**22**) (Todd *et al.*, 1993).

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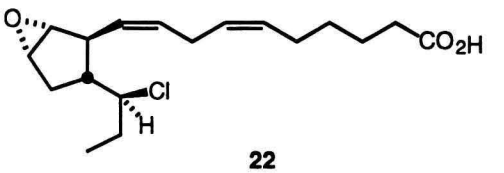
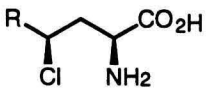


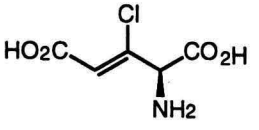

**22**

## Amino Acids and Peptides

Several simple halogenated amino acids and peptides have been found in microorganisms such as *Streptomyces* and *Pseudomonas*. Some are shown here (**23-27**).




**23** R = Cl
**24** R = $CH_3$

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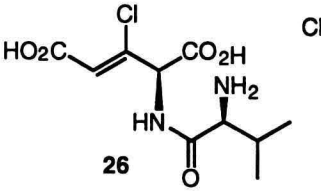
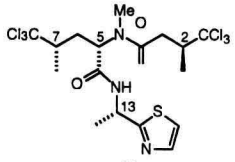



**26**


**27**

The marine sponge *Dysidea herbacea* has proven to be a rich source of novel amino acid and peptide-derived metabolites such as dysidin and dysidenin (**28**). These trichloromethyl compounds may be a source of chloroform in the oceans. Cryptophycin A (**29**) is one of many related *Nostoc* sp. blue-green algae metabolites with excellent anticancer activity against solid tumors (Golakoti *et al.*, 1995). The *threo*-4-chlorothreonine amino acid is found in several *Pseudomonas syringae* cyclic peptides (Fukuchi *et al.*, 1992). The fungal pathogen *Periconia circinata* produces several interesting chlorine-containing peptides such as peritoxin A (**30**) (Macko *et al.*, 1992).

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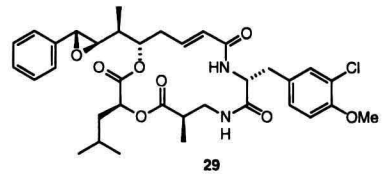


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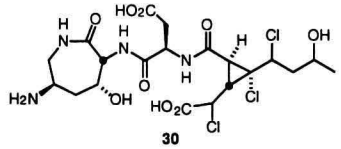
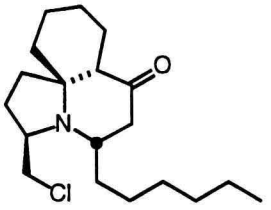



**30**

## Alkaloids

Despite the enormous number of known terrestrial plant alkaloids, only a few halogen-containing examples have been discovered. Some early examples include jaconine (*Senecio jacobaea*), doronine (*Doronicum macrophyllum*), lolidine (*Lolium cuneatum*), and acutumine (*Sinomenium acutum*). The Tasmanian ascidian *Clavelina cylindrica* produces the novel alkaloids cylindricine A (**31**) and B (Blackman *et al.*, 1993). The Asian folk medicine plant *Houttuyniae cordata* has yielded 7-chloro-6-demethylcepharadione B (**32**) (Jong and Jean, 1993), and epibatidine (**33**), which is a potent analgesic, is secreted by the Ecuadorian frog *Epipedobates tricolor* (Spande *et al.*, 1992).

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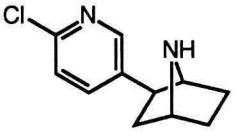
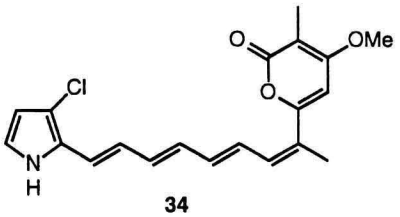



**33**

## Heterocycles

The high reactivity of heterocycles such as pyrroles and indoles towards electrophiles portends the large number of naturally occurring halogenated electron-rich heterocycles. Several chlorinated pyrroles are produced by *Pseudomonas* spp., such as pyoluteorin and pyrrolnitrin, and the optically active neopyrrolomycin is found in cultures of a *Streptomyces* sp. The fungus *Auxarthron umbrinum* produces rumbrin (**34**), which may be useful in the treatment of ischemia (Yamagishi *et al.*, 1993). The sponge *Phorbas aff. clathrata* contains four chlorinated phorbazoles (e.g., **35**) (Rudi *et al.*, 1994), and a set of novel pyralomicins, such as **36**, is produced by *Actinomadura spiralis* (Kawamura *et al.*, 1995).

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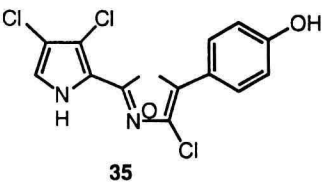


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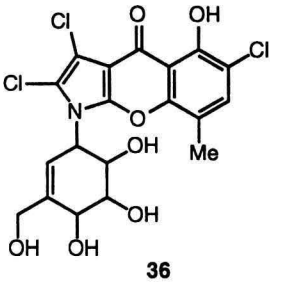
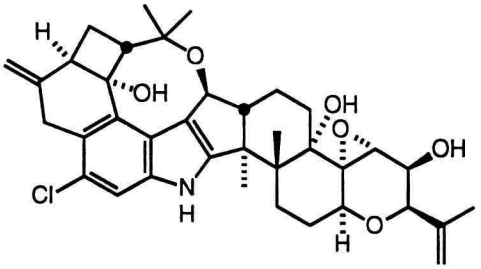



**36**

Halogenated indoles are widespread in living systems. The simple 3-chloroindole is found in the acorn worm *Ptychodera flava laysanica*, and the New Zealand red alga *Rhodophyllis membranacea* produces eight novel chlorinated indoles including 2,3-dichloro-7-bromo-indole. 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. 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 (Brown *et al.*, 1992). The blue-green alga *Hapalosiphon fontinalis* is the source of a dozen chlorinated isonitriles, and related compounds are produced by *Fischerella* spp. blue-green algae (Park *et al.*, 1992). The fungus *Penicillium crustosum* produces three 6-chloroindole penitrem metabolites of almost incredible molecular complexity (e.g., penitrem A (**37**)). The bryozoan *Chartella papyracea* has yielded the stunningly complex chartelline A (**38**) and several related halogenated indoles. In contrast, the bryozoan *Amathia convoluta* contains four indoles such as convolutamydine B (**39**) (Zhang *et al.*, 1995). More recently, the bryozoan *Securiflustra securifrons* has been found to contain four chlorinated securamines, e.g., **40** (Rahbaek *et al.*, 1996).

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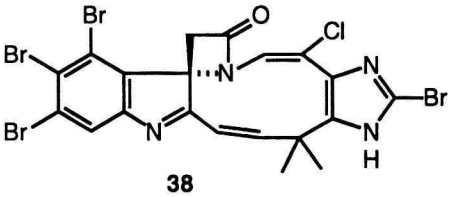


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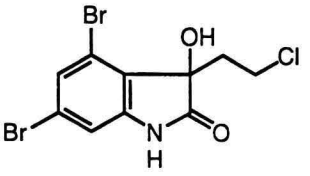


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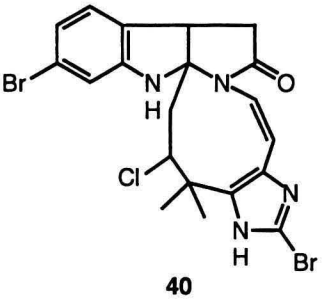
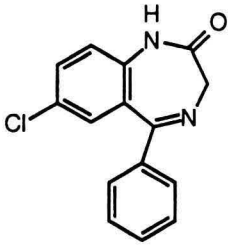



**40**

Surprisingly, seven chlorine-containing benzodiazenes, such as **41**, are found in wheat and potato tubers (Klotz, 1991), and benzodiazepines, including several chlorine-containing examples, are found in human and animal brains (Medina *et al.*, 1993). There is strong evidence of the *in vivo* formation of these chlorinated benzodiazepines in the mammalian brain. Several nucleic acid bases contain chlorine, such as **42** from *Streptomyces rishiriensis*, and kumusine (**43**) from a *Theonella* sp. sponge (Ichiba *et al.*, 1995) and the sponge *Trachycladus laevispirulifer* (Searle and Molinski, 1995).



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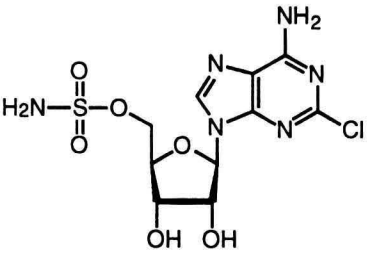

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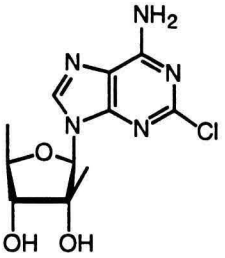

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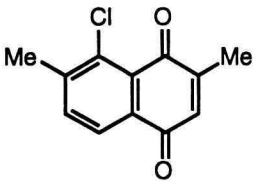
## Macrolides

Several halogen-containing macrolides are known. Chlorothricin and its derivatives are produced by *Streptomyces* spp. and the well-known maytansinoids are found in numerous microorganisms. The simpler monorden (radicidol) is produced by *Monosporium bonorden* and *Nectria radicicola*, and the related 6-chlorodehydrocurvularin was extracted from the fungus *Cochliobolus spicifer* (Ghisalberti and Rowland, 1993). A collection of remarkably active antitumor sponge metabolites, the spongistatins, have been discovered in *Spirastrella spinispirulifera*, some of which contain the chlorovinyl moiety (Pettit *et al.*, 1993).

## Quinones

Many aromatic quinones of varying complexity contain chlorine and a few contain bromine. The simple 8-chlorochimaphilin (**44**), which has antibiotic activity, was recently isolated from *Moneses uniflora* (Saxena *et al.*, 1996). A series of eight chlorinated napyradiomycins (e.g., **45**) have been isolated from *Chainia rubra* (Hori *et al.*, 1993) and four extraordinary chloropalmarumycins (e.g., **46**) were found in the West Borneo forest soil microbe *Coniothyrium* sp. (Krohn *et al.*, 1994).



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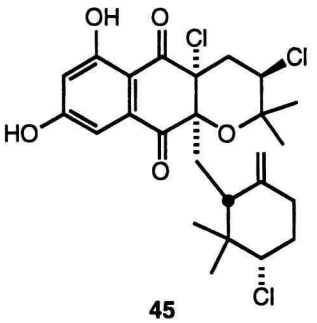

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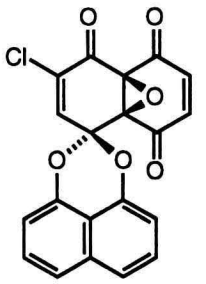

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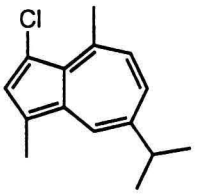
## Aromatic Compounds

Although most of the known halogenated 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*) and a deep sea gorgonian has yielded azulene **47**. The novel nostocyclophanes (e.g., **48**) are produced by the blue-green alga *Nostoc linckia* (Chen *et al.*, 1991), and 3-chloroanthranilic acid is found in cultures of *Pseudomonas aureofaciens*.

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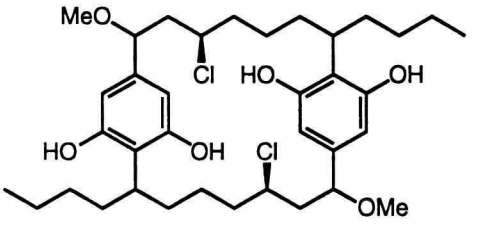


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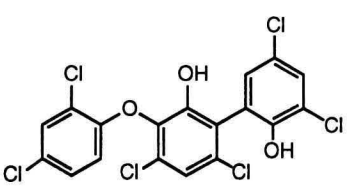
## Phenols

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 and at least a dozen species of ticks biosynthesize 2,6-dichlorophenol as a sex pheromone. Chloride labeling studies confirm the biosynthesis of this compound within the insect. Amudol is found in *Penicillium martinsii*, and several other chlorine-containing benzyl alcohols and benzaldehydes are produced by white-rot and other fungi (Spinnler *et al.*, 1994). There is also mounting evidence that 2,4,6-trichlorophenol is a natural product of soil microbes (Hodin *et al.*, 1991). The Florida acorn worm *Ptychodera bahamensis* contains four chloro- and bromophenols (Corgiat *et al.*, 1993). Some chlorinated tyrosines are found in the proteins of locusts and molluscs, where they are believed to improve adhesion between protein fibers and sheets. Several chlorine-containing diphenyl ethers have been reported, mainly from fungi and algae. The freshwater fungus *Kirschsteiniothelia* sp. produces **49** (Poch *et al.*, 1992), and the terrestrial blue-green alga *Fischerella ambigua* has afforded ambigol A (**50**) (Falch *et al.*, 1993). This latter compound inhibits HIV reverse transcriptase. A number of chlorinated fucols have been extracted from the brown alga *Analipus japonicus*. The toxic mushroom *Russula subnigricans* contains seven chlorinated russuphelins, such as russuphelol (**51**) (Ohta *et al.*, 1995).



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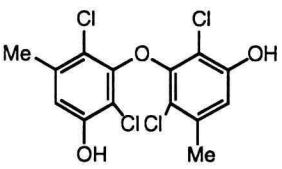

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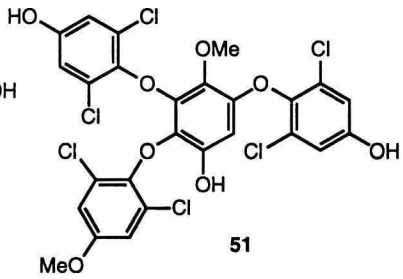

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Other natural chlorine-containing phenolic derivatives include transformed tyrosines from sponges, depsides and depsidones from lichens, and xanthones and anthraquinones from lichens and fungi. A remarkable observation is the detection of chlorotyrosine in low-density lipoproteins isolated from human atherosclerotic lesions (Heinecke, 1996). Perhaps the most medicinally important organochlorine compound is vancomycin, the glycopeptide antibiotic and the drug of choice to treat methicillin-resistant *Staphylococcus aureus* infections, particularly those that occur in hospitals. Most of the 200 known glycopeptides contain chlorine (Nagarajan, 1993).

## Miscellaneous

A fitting conclusion to this brief survey is to mention the isolation of prymnesin-2 from the red tide alga *Prymnesium parvum* (Igarashi, *et al.*, 1996). This enormous organohalogen, $C_{96}H_{136}Cl_3NO_{35}$, is a potent ichthyotoxin and the first red tide toxin found to contain chlorine.

## Summary

The number of reported organohalogens from living organisms continues to increase. These discoveries result from our advances in collection, isolation, bioassay, and spectroscopic identification techniques. The total number of 2,730 natural organohalogen compounds can be divided into 1,600 organochlorines, 1,570 organobromines, 90 organoiodines, and 20 organo-fluorines. Since many of these compounds, especially those from marine sources, contain both chlorine and bromine, these are included in both categories. As only a small percentage of living organisms have been examined for their chemical content, it is certain that a large number of new natural organohalogen compounds is awaiting discovery. Moreover, since mammals, including humans, utilize in vivo halogenation in white blood cells as part of the immune process, it is only a matter of time before additional organohalogen compounds are found to occur naturally in humans.

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