

Natural Halogenated Alkanes, Cycloalkanes and Their Derivatives

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Abstract

Simple halogenated alkanes and their derivatives comprise relatively large group of natural compounds which were discovered in cyanobacteria, algae, phytoplankton, fungi and plants. The structures of more than 100 compounds are considered.

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INTRODUCTION

Halogen-containing (F^- , Cl^- , Br^- and I^-) compounds are widespread in nature. They are synthesized by marine and land plants, bacteria, fungi, insects, marine organisms, even by mammals. Along with halogen-containing compounds generated by living organisms, a large number of halogenated compounds was found to be the products of abiotic origin. These compounds include the majority of halogenated hydrocarbons and their derivatives formed as a result of various geothermal processes, such as eruptions (both on land and under water) [1–12], karst phenomena [13–15], and some meteorological processes (lightning). It should be mentioned that many halogen-containing compounds are the products of human vital activity and are detected in various animal species [16–19].

Marine organisms, first of all algae, invertebrates, cyanobacteria and microorganisms, generate mainly brominated metabolites, chlorinated ones are more rare, and iodine-containing ones are the rarest [20–24]; fluorinated metabolites were not detected in marine organisms. Such a ratio between the brominated and chlorinated compounds is not quite clear since the content of Cl^- ions is several orders of magnitude higher than that of Br^- ions. The concentration of chloride ions in the ocean is 19.000 mg/l, while that of bromide ions is only 65 mg/l [25, 26]. Iodine and bromine in the free state were discovered in some species of algae and invertebrates. For instance, such algae as *Asparagopsis armata*, *Falkenbergia doubleti* and *Bonnemaisonia asparagoides* contain free iodine [27]. Fifty species of cyanobacteria (Cyanophyta), green (Chlorophyta), brown (Phaeophyta) and red (Rhodophyta)

contain free iodine [28], while free bromine was detected in 46 species of sea sponges [29]. Total content of halogens (per dry mass) in algae can be 0.64 % in *Laurencia pacifica* and 0.29 % in *Plocamium pacificum* [30]. Though the concentration of F⁻ ions in sea water is not high and makes only 1.3 mg/l [25], sea sponge *Halichondria moori* contains potassium fluorosilicate (K₂SiF₆) in the amount of 10 % of the dry mass [31]. Though this sponge contains much fluorine, no organic metabolites containing fluorine were detected in this sponge. Fluorine was not detected also in the sponges belonging to this family.

ALKANES OF ABIOTIC ORIGIN

As we have already mentioned above, halogenated alkanes of abiotic origin include compounds discovered in volcanic gases or in sea water. For example, simple halogenated hydrocarbons, such as CH₃Br [32–34], CH₃I [32, 33], Cl₂C=CHCl [35], Cl₂C=CCl₂ [36, 37], CFCl₃, CF₂Cl₂, CHFCl₂ [35–37], CHF₂Cl, F₂C=CF₂, FCIC=CF₂, CCl₂FCClF₂, CF₃CF=CF₂, [35], CF₄ [38, 39], (CH₃)₂SiF₂ [36, 37], were discovered in gases evolving during eruptions.

Some halogenated alkanes – CH₃Br [40], CH₃I [41–43], CH₂Br₂ [42, 44–46], CHBr₃ [46–50], CH₂ClBr [45, 49], CH₂ClI [45, 49, 51], CH₂I₂ [44, 45, 51, 52], CHCl₂Br, CHClBr₂ [42, 44–46], CH₃CH₂CH₂I, CH₃CH₂CH₂CH₂I [51–53], CH₃CH₂CH₂CH₂CH₂I, CH₃CH₂CH₂CH₂CH₂Br [53], CH₃CH₂CH(CH₃)I [51] и CH₃CCl₃ [50] – were found in the sea water of the Atlantic, Indian and Pacific oceans, as well as in the water of Arctic and Antarctic, where there is no direct effect of anthropogenic action. The majority of authors of the cited works believe that the above-mentioned halogenated alkanes are of abiotic origin; however, some authors think that these compounds are the products of vital activity of marine microorganisms and/or algae [17, 18, 21]. Many bromine- and iodine-containing simple alkanes were also found in algae.

ACYCLIC ALKANES AND THEIR DERIVATIVES

Chloromethane (CH₃Cl) is generated by some species of parasitic fungi causing wood putre-

faction: *Fomes conchatus*, *F. occidentalis*, *F. pomaceus*, *F. ribis*, *F. rimosus* and *F. robinia* [54], and also by the fungi belonging to the *Phellinus* genus: *P. ignarius*, *P. lundelli*, *P. pomaceus*, *P. ribis*, *P. occidentalis*, *P. pachyploes*, *P. pini*, *P. populicola* and *P. trivialis* [55–58]. Fungi *Inonotus andersoni* and *Inonotus hispidus* [57] generate chloromethane which accounts for 75–90 % of all the volatile components. Among 63 species of parasitic fungi causing wood putrefaction and belonging to *Phellinus*, *Hymenochaete*, *Fomitoporia*, *Omnia*, *Inonotus* and *Phaeolus*, only 34 generate chloromethane [57]. Among 27 fungi species of Ganodermataceae and Polyporaceae orders, only one species, namely, *Fomitopsis cytisina*, was able to include chloromethane in other metabolites [57]. These results indicate that wood putrefaction is due to the evolution of chloromethane by fungi, especially by those of *Phellinus* and *Inonotus* geni, which are widespread in tropical and subtropical forests [55, 57, 58].

Chloromethane was also detected in *Agaricus bisporus* fungi [59], in sea phytoplankton [53], in tubers of *Solanum tuberosum* plant [60], in *Endocladia muricata* alga [61], in giant kelp *Macrocystis pyrifera* [62], in pearlwrorts *Biflustra perfragilis* living near the island of Tasmania (Australia) [63], in cedar and cypress wood [64], and in *Mesembryanthemum crystallium* plant [61].

Dichloromethane (CH₂Cl₂) was discovered in in pearlwrorts *Biflustra perfragilis* living near the island of Tasmania (Australia) [63], in sea kelp macrophytes *Ascophyllum nodosum*, *Fucus vesiculosus*, green algae *Enteromorpha linza* and *Ulva lacta*, and in red algae *Gigartina stellata* [53].

The presence of chloroform CHCl₃ was detected in wood moss, northern white cedar [64], in barley, lemons and oranges [36], in *Cantharellus cibarium* fungi [65], in land plants *Farsetia aegyptia* and *F. ramosissima* [66], in fruit of plants: *Achras sapota* [67], *Sergia leicens* [68] and *Basella rubra* [69]. Sea algae *Asparagopsis taxiformis*, *A. armata* [69] and *Meristiella gelidium* [70] generate chloroform and other chlorine-containing metabolites. Tetrachloromethane CCl₄ was discovered in some land plants [66].

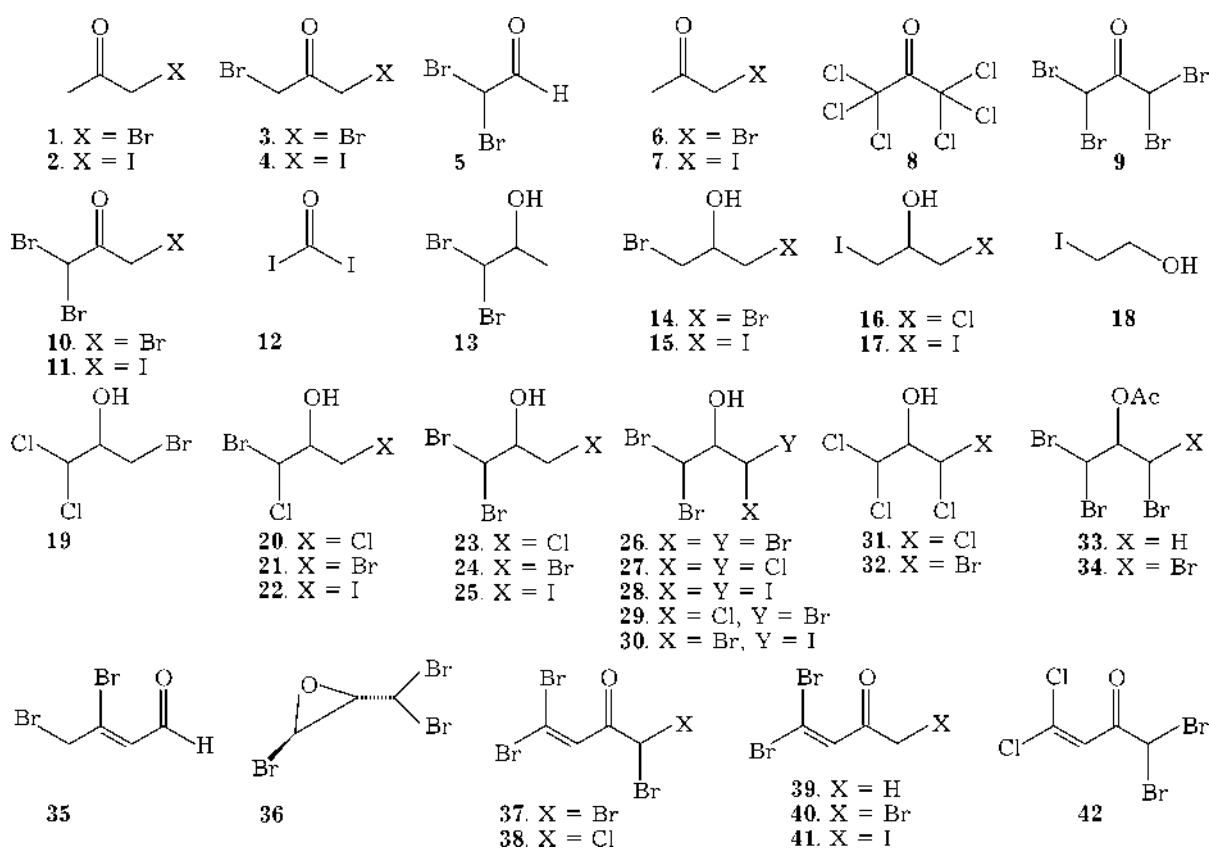
Many algae generate halogenated metabolites and can accumulate them in rather large amounts from seawater. For example, the content of methyl iodide CH_3I in *Laminaria* sp. alga is 1000 times higher than in the oceanic water [71]. Many other sea species of red, green and brown macrophyte algae growing near the coast of South California generate methyl iodide [72]. It is interesting that a number of parasitic fungi of *Fomes* [54] and *Phellinus* [58] geni transform bromide and iodide ions into methyl bromide and methyl iodide, respectively. Bromoform CHBr_3 was detected in seawater; however, its main producers are algae and phytoplankton. For instance, about 80 % of all the halogenated metabolites generated by *Asparagopsis taxiformis* alga growing near the Hawaiian Isls is bromoform [73, 74].

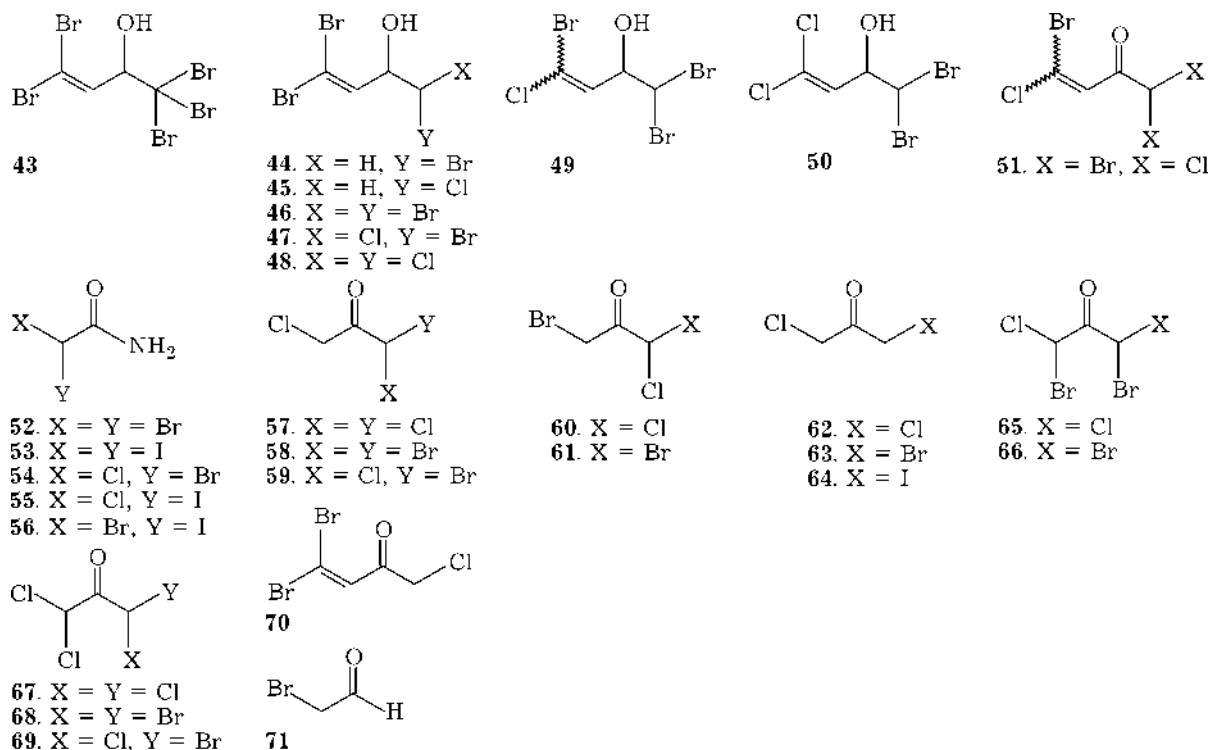
Halogenated alkanes, such as CH_3Cl , CH_3Br , CH_3I , CH_2Br_2 and CHBr_3 , are generated by the brown alga *Macrocystis pyrifera* [62, 72, 75]. Brown algae *Eisenia arborea*, *Egrecia menziesii*, *Custoseria osmundacea* and *Laminaria farlowii* generate CH_3I , CHBr_3 and CH_2Br_2 [72, 75], while *Prorygophora californica* and *Dictyota bingha-*

mie contain only CH_3I [72, 75]. Brown alga *Fucus Vesiculosus* generates CH_2Br_2 , CHBr_3 , CHBr_2Cl , CH_2Cl_2 , CHBrCl_2 , CH_2I_2 , CH_3I and CH_2ICl [52, 53]; *Ascophyllum nodosum* generates CHBr_3 , CHBr_2Cl , CH_2Cl_2 , CHBrCl_2 , CH_2I_2 , CH_3I [53]. Halogenated alkanes CH_2I_2 , CH_3I , CHBr_3 , CHBr_2Cl , CH_2Br_2 and CHBrCl_2 were detected in *Fucales sargassum* [44, 45].

Red algae *Corallina officinales*, *Pterocladia capillacea* and *Rhododymenia californica* synthesize three halogenated alkanes: CH_3I , CHBr_3 and CH_2Br_2 [72]; *Bonnemaisonia hamifera* synthesizes only CHBr_3 [76]. *Meristiella gelidium* contains CH_3I and CH_2ClI [70], while *Gigartina stellata* – the same alkanes except CH_2ClI [53].

Two species of the *Asparagopsis* genus (*A. armata* and *A. taxiformis*) generate approximately the same set of halogenated alkanes: CH_3I , CH_2Br_2 . In addition to the indicated halomethanes, *A. taxiformis* alga contains also CCl_4 , CHBrClI , CH_2BrI and CHI_3 [69, 73, 74]. Red alga *Asparagopsis taxiformis*, which is spread near the Hawaiian Isls (USA), generates a unique set of halogenated organics (1)–(61) [73, 74, 77, 78]. The Mediterranean red alga





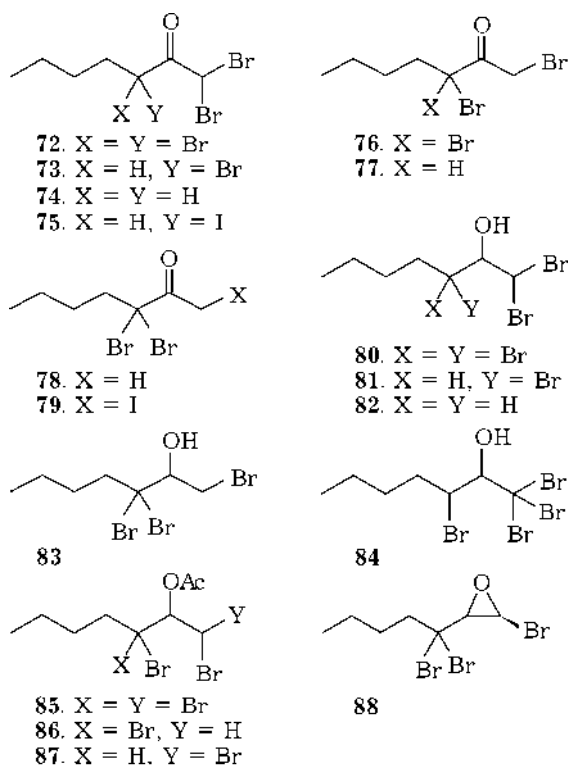
Asparagopsis armata and *Asparagopsis taxiformis* from the Californian Bay (USA) generate halogenated metabolites (62)–(71) [69, 79].

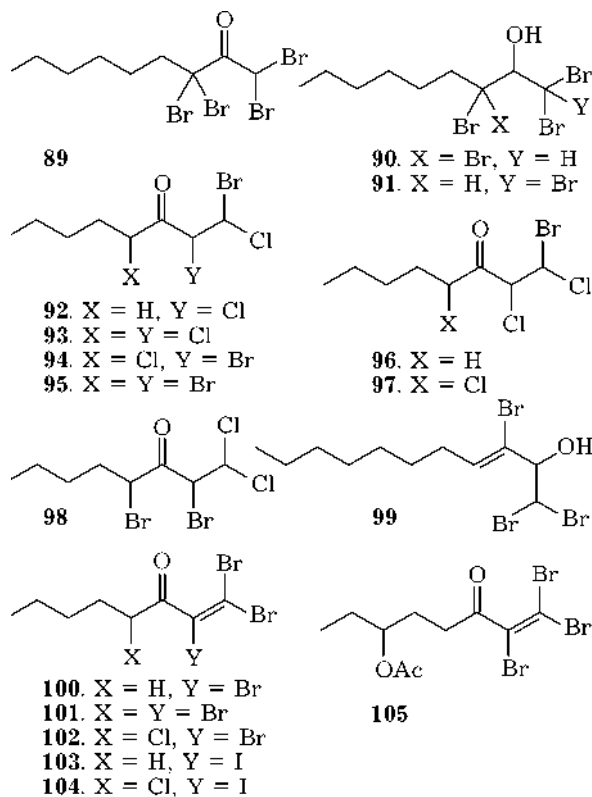
Halogenated metabolites (72)–(88) were isolated from the red alga *Bonnemaisonia hamifera* [80–82]. Two other species of the same genus, *B. nootkana* and *B. asparagoides* [82, 84] generate metabolites (89)–(91) and (92)–(98), respectively [82, 83]. Red algae *Delisea fimbriata* [85] and *D. pulchra* [86] contain compounds (99)–(105).

Three bromine-containing ketones (106)–(108) were isolated from red alga *Ptilonia australasica*, dichloroacetamide (109) was discovered in the extract of red alga *Marginisporium aberrans* [87]. Halogenated metabolites (110)–(114) are generated by the Australian red alga *Falkenbergia rufolanosa* [88].

The most intense works of the recent years dealing with investigation of the occurrence of halogenated alkanes in sea macrophyte algae which are widespread in the Antarctic and Arctic water were carried out by the author of [89–92]. These investigations, which have made a substantial contribution into our notions concerning the ability of sea algae to synthesize halogenated alkanes were summarized in the review [89]. On the basis of investigation of more than 50 species of alga species, the

author concluded that the main generators of halogenated alkanes in polar regions are brown algae. For example, the Antarctic brown algae *Adenocystis utricularis*, *Ascoseira mirabilis*, *Cystosphaera jacquinotii*, *Desmarestia antarctica*, *D. anceps*, *D. menziesii*, *Halopteris obovata*,





Himantothalpus gradifolius and *Phaeurus antarcticus* generate CH_2ClI , CH_2I_2 , CHBrCl_2 , CHBr_2Cl , CH_2Br_2 , CHBr_3 and $1,2\text{-C}_2\text{H}_4\text{Br}_2$ [92]. The concentration of halogenated alkanes is 3.9 mg/g (calculated with respect to the dry mass of the alga) in *Desmarestia anceps*, 1.3 mg/g in *D. menziesii* alga, 0.84 mg/g in *Cystosphaera jacquinotii* and 0.3 mg/g in *Himantothalpus gradifolius* alga [92]. High content of CH_2ClI and CHBrCl_2 was discovered for the first time in the goldish alga *Antarctosaccion applanatum* (Chrysophyta section). Red and green algae generate the same alkanes but in substantially smaller amount.

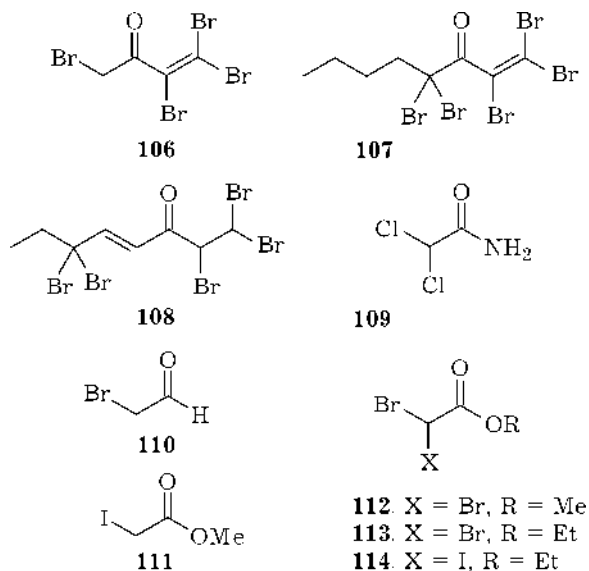
High content of halogenated alkanes is also characteristic of the brown algae growing in the Arctic seas. For example, alkanes CH_2ClI , CH_2I_2 , CHBrCl_2 , CHBr_2Cl , CH_2Br_2 , CHBr_3 and $1,2\text{-C}_2\text{H}_4\text{Br}_2$ were detected in the following species of brown algae: *Alaria* sp., *Chorda filum*, *Ch. tomentosa*, *Chordaria flagelliformis*, *Fucus distichus*, *Dictyosiphon foeniculaceus*, *Pilayella littoralis*, *Laminaria digitata*, *L. saccharina*, *L. Solidungula*. The concentration of halogenated alkanes was lower than that in the Antarctic species of brown algae, varying within 0.15–0.30 mg/g of the dry mass [91].

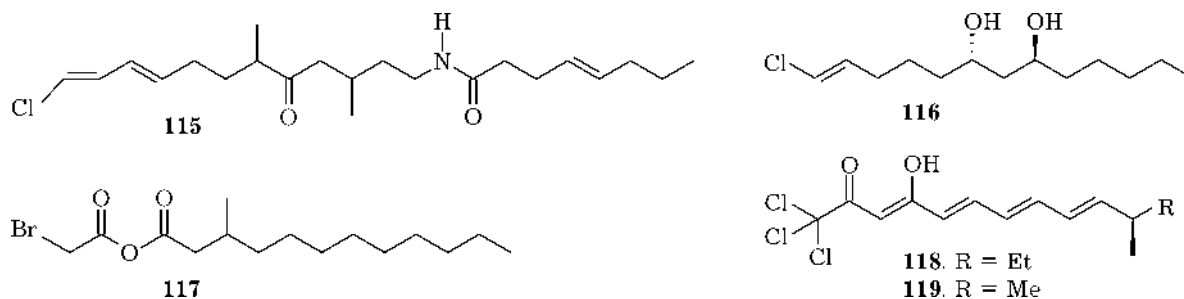
Red algae contained a small amount of halogenated alkanes, while high level of alkanes CH_2ClI , CHBrCl_2 , CHBr_2Cl , CH_2Br_2 , CHBr_3 and $1,2\text{-C}_2\text{H}_4\text{Br}_2$ was discovered the green algae *Urospora penicilliformis*, *Blidingia minima*, *Acrosiphonia sonderi*, *Monostroma arcticum*, *Enteromorpha compressa* and *Chaetomorpha melagonium* [91].

A number of green algae from the tropic seas also generate halogenated alkanes. For instance, *Ulva* sp. and *Enteromorpha intestinales* [72] generate CH_3I , CHBr_3 and CH_2Br_2 ; *Penicillus capitalus* generate only one alkane CHBr_3 . The *Enteromorpha linza* and *Ulva lacta* algae generate the same compounds: CHBrCl_2 , CHBr_2Cl , CH_2Br_2 , CHBr_3 , CH_2Cl_2 , CH_2I_2 and CH_3I [53].

According to the data obtained by the researchers from the Stockholm University [93], tropical algae *Hypnea spinoides*, *Grateloupia doryphora* and *Falkenbergia hillebrandii* (the Canary Isls, Spain) more actively generate halogenated alkanes (CH_3I , CHCl_3 , CH_3CCl_3 , CCl_4 , CHBrCl_2 , CH_2Br_2 , $\text{CHCl}=\text{CCl}_2$, $\text{CH}_3\text{CHICH}_3$, CH_2ClI , CHBr_3 , $\text{CH}_2\text{CH}_2\text{CHICH}_2\text{CH}_3$, $\text{Cl}_2\text{C}=\text{CCl}_2$, CHBr_2Cl , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$ and CH_2I_2) in daytime from 10 A.M. till 14 and at the temperature of 28 °C. At night and at lower temperature, the biosynthesis of alkanes decreases by a factor of 2–3.

Some sea microalgae isolated from phytoplankton are also the source of halogenated alkanes. For example, *Nitzschia* sp. and *Porosira glacialis* contain the same set of halogen-sub-





stituted alkanes: CH_2ClI , CHBr_2Cl , CHBr_3 and CH_2Br_2 [94]. The compounds CH_3Br , CH_2BrCl , CHBrCl_2 , CHBr_2Cl , CHBr_3 and CH_2Br_2 are the products of the vital functions of *Nitzschia stellata* and *Porosira pseudodenticulata* [95].

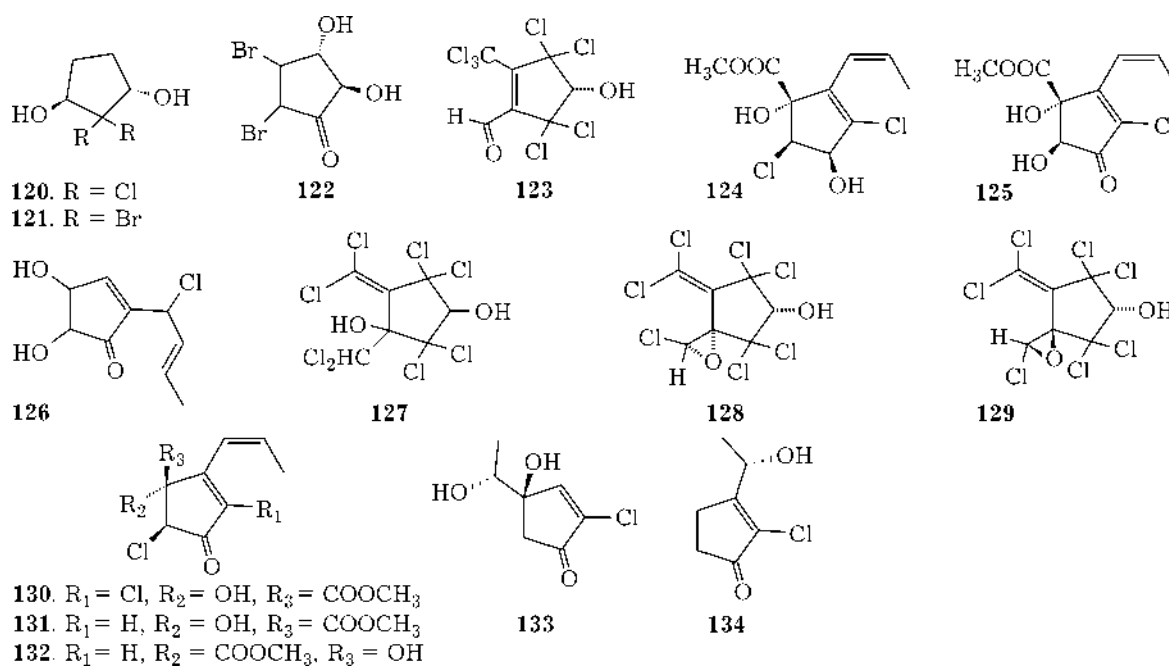
A new chlorine-containing amide pitiamide A (**115**) was isolated from a symbiotic mixture of cyanobacteria *Lyngbya majuscula* and *Microcoleus* sp., which naturally inhabit *Porites cylindrical* coral near the Guam Is. (USA) [96]. Another metabolite, 1-chlorotridec-1(*E*)-en-6(*R*)-diol (**116**), is generated by cyanobacteria *Lyngbya majuscula* and a mixture of cyanobacteria *Schizothrix caliciola* and *Oscillatoria nigroviridis* [97]. This metabolite exhibited high activity against pathogenic microorganism *Mycobacterium smagmatis*.

Bromine-containing metabolite (**117**) was the first halogen-containing compound isolated from normal human cerebrospinal fluid [98]. It has physiological functions of hormones.

Two new polyenes, neocarzilene A (**118**) and B (**119**), are generated by *Stroptomyces carzinostaticus* fungus [99]. Neocarzilene B (**119**) exhibited high activity against the leukemia cells K562.

ALICYCLIC ALKANES

Halogenated alicyclic alkanes comprise a small group of natural metabolites. Caldariomycine (**120**) was isolated for the first time in 1940 from *Caldariomyces fumago* fungus [100]. Its bromide-containing analog (**121**) is generated by the same fungus when bromide ion is present in the incubation mixture [101]. The structure of (**120**) was confirmed by synthesis [102]. Brominated dihydrofulvene (**122**) was discovered in the Australian alga *Vidalia spiralis* [103]. The *Mollisia* fungus generates inhibitors of phosphodiesterases. For instance, compounds (**123**), (**127**)–(**129**) inhibit phosphodiesterases KS-



504E, KS-504D, KS-504B and KS-504A, respectively [104, 105].

The derivatives of cyclopentanone (**124**), (**125**), (**130**)–(**132**) are generated by several different fungi. The *Cryptosporiopsis* sp. contains metabolite (**124**) [106], and *Periconia macrospinoso* fungus contains chlorocyclopentadiol (**125**) [107]. Cryptosporiopsine (**130**) and compounds (**131**), (**132**) were detected in *Sporormia affinis* fungus [108]. The same metabolites (**130**)–(**132**) are generated by *Periconia macrospinoso* [107], *Cryptosporiopsis* sp. and *Phialophra asteris* f. sp. *helianthi* fungus [110]. Cryptosporiopsine (**130**) inhibits the growth of pathogenic sunflower fungus *Sclerotinia sclerotiorum* [110]. A new biologically active cyclopentenone (**126**) inhibiting the development of carcinoma was isolated from the fungus related to *Ascomycota* [111]. Trichodenones B (**133**) and C (**134**) are generated by microorganism *Trichoderma harzianum* (OUPS-N115 strain), which is a symbiont of the sea sponge *Halichondria okadai* [112].

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