Review

Natural halogenated fatty acids: their analogues and derivatives

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Abstract

A comprehensive survey has been made of all fatty acids containing halogen atoms covalently bonded to carbon and which are deemed as naturally occurring. Generally thought to be minor components produced by many different organisms, these interesting compounds now number more than 300. Recent research, especially in the marine area, indicates this number will increase in the future. Sources of halogenated fatty acids include microorganisms, algae, marine invertebrates, and higher plants and some animals. Their possible biological significance has also been discussed © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

This review is intended as a comprehensive survey of fatty acids and/or their derivatives possessing carbon–halogen covalent bonds, which have been obtained from living organisms. Fatty acids constitute the most abundant class of natural compounds and are included in the composition of complex lipids. The fatty acids differ in the number of olefinic bonds, extent of branching, the length of the hydrocarbon chain, and the number of functional groups. Halogenated fatty acids which are one of the most interesting groups among the naturally occurring halogen compounds are insufficiently sighted in the literature [1–4]. References are introduced, which encompass different groups of organisms from microorganisms to the highest plants and animals [5]. This survey is restricted to halogen compounds isolated from fungi [6,7], higher plant [8], marine algae [9].
[9,10], marine organisms [11–18], fishes and molluscs [19–21], and/or integrated data on all groups of organisms [4,5,22,23].

The present review covers the literature to September 2001 and lists the known structures of more than 200 fatty acids and their analogues and derivatives containing covalently bound halogens (F, Cl, Br, and I, and also both Cl and Br) and which may be considered naturally occurring.

Our preliminary review describing several aspects of natural halogenated carboxylic acids has been published in New Russian Chemical Journal known in the West as Chemistry of Sustainable Development [1] published by The Russian Academy of Sciences.

2. Fluorinated fatty acids

Fluorinated secondary metabolites are rare in nature [1,4,5]. Marais [24,25] was the first to identify fluoracetic acid 1 from the South African plant Dichapetalum cymosum growing in the Transvaal region, in 1943. The young leaves of this plant can accumulate fluoroacetate up to 2500 μg^{-1} dry weight [26,27]. Recently, O’Hagan et al. [28] reported that young leaves and seeds of D. braunii (Dichapetalaceae) from south-western Tanzania have the highest level of fluoroacetate, up to 8000 μg^{-1} dry weight. High concentrations of fluoroacetate also occur in the leaves: D. barteri [29], D. dejlexum [30,31], D. heudelotti [32], D. guineense [33], D. macrocarpum [30], D. michelsonii [34], D. mossambicense [30,31], D. ruhlandii [35], D. venenatum [36], D. tomentosum [29], D. toxicarium [37], and has also been identified in Spondianthus preussi from West Africa [31]. The Australian plants Acacia georginae growing in Queensland also accumulated fluoroacetate up to 250–400 μg^{-1} [38,39].

Peters et al. [40] isolated ω-fluorooleic (ω-fluoro-cis-Δ^{9}-octadecanoic) acid 2 from the seed oil of D. toxicarium in 1959. The presence of other ω-flouro fatty acids such as ω-fluorocapric 3, ω-fluoromyristic 4, and ω-fluoropalmitic 5 acids has also been confirmed by gas chromatography–mass spectrometry (GC–MS) and NMR [41–43].

![Chemical structures](image)

The biosynthesis of ω-fluorofatty acids by D. toxicarium was demonstrated by Walsh et al. [44]. Fluoroacetyl-CoA 6 was determined as the starter unit in the biosynthesis all ω-fluorofatty acids and other fluoro-containing metabolites such as fluorocitrate 7 (Scheme 1). The stereochemistry of the citrate synthase reaction with fluoroacetyl-CoA 6 has been studied in detail [45–47]. A biosynthetic mechanism as indicated on Scheme 1 was confirmed by isolation of 18-fluoro-9,10-epoxystearic 8 [48] and threo-18-fluoro-9,10-dihydroxystearic 9 acids from the seed oil of D.
toxicarium [49]. In addition, ω-fluoro-palmitoleic (trace), -linoleic (9.6%), -arachidic (trace) and eicosenoic (trace) acids have also been isolated [48]. The presence in plants of ω-fluoro fatty acids and other fluorine-containing natural compounds were recently reviewed by Harper and O’Hagan [50].

Scheme 1. Possible biosynthesis of ω-fluorinated fatty acids in *Dichapetalum toxicarium*. 
Recently Christie et al. [51,52] characterized the picolinyl ester and 4,4-dimethyloxazoline derivatives of the $\omega$-fluoro fatty acids isolated from the seed oil of $D. toxicarium$ by GC–MS.

The picolinyl esters gave mass spectra that permitted determination of the positions of double bonds, and confirmed that the fluorine atom was on the terminal carbon in each instance. By the use of these techniques, a number of novel unsaturated $\omega$-fluoro fatty acids were identified in the $D. toxicarium$ oil, i.e. $\omega$-fluoro-7-16:1 10, 9-16:1 11, 18:0, 9-18:1, 9,12-18:2 12, 20:0, 9-20:1 13 and 11-20:1 14, in addition to earlier known $\omega$-fluorinated acids.

2.1. Desaturation of fluorinated fatty acids

A study to produce modified seed oil [53] by introduction by chemical means of cis double bonds into fluorinated fatty acids was reported [54,55]. Only (E)-fluoroalkenic compounds were obtained when racemic 9- and 10-fluoro fatty acids were cultivated with $Saccharomyces cerevisiae$ $\Delta^9$ desaturase (Scheme 2) [54]. Desaturation of (S)-9-fluorostearoyl-ACP using stearoyl-ACP $\Delta^9$ desaturase yielded mainly (E)-9-fluoroalk-9-enic product, while desaturation of (R)-9-fluoro-stearoyl-ACP gave the novel (Z)-fluoroalk-9-ene and (Z)-fluoroalk-10-ene [55].

Scheme 2. Desaturation of 9- and 10-fluoropalmitic acid by $Saccharomyces cerevisiae$ $\Delta^9$ desaturase.
2.2. Synthesis of fluorinated analogues of unsaturated fatty acids

(9Z,11E)-13-Hydroxy-9,11-octadecadienoic acid (13 HODE) called coriolic acid 15 is known as the self-defense agent against rice blast disease [56]. It displays unique calcium ionophoric properties [57]. It is also present in sera of patients with familial Mediterranean fever and may have a role in its pathogenesis [58]. Furthermore it acts as a vessel wall chemorepellant [59]. It is an inhibitor of platelet aggregation [60] and platelet adhesion in human endothelium cell culture [61], and appears involved in tumor cell adhesion [62]. The first synthesis of fluorinated analogues 16 and 17 of coriolic acid were reported by Gree et al. [63] (Scheme 3). The authors described a very short and efficient synthesis of monofluorinated analogs of lipid mediators.

Two other fluorinated derivatives 18 and 19 of coriolic acid were synthesized by Heck-type reaction of fluoroalkenylidonium salts (Scheme 4) [64].

Satter and Haufe [65] converted alk-1-enoic acids into 11–13-membered (ω-1)-fluoroalkan-ω-olides 20–22 with about 10–15% of the corresponding diolides via ω-bromo-(ω-1)-fluoroalkanoic acids (Scheme 5).

Scheme 3. Synthesis of novel 13-fluoro coriolic acid analog 16 and (5Z,7E)-9-fluoro-5,7-tetradecadienoic acid 17 was achieved [63].

Scheme 4. Synthesis of (9E,11E)-9-fluoro-13-oxo-9,11-octadecadienoic 18 and (9E,11E)-9-fluoro-13-hydroxy-9,11-octadecadienoic 19 acids were reported [64].
Difluoro- and trifluoromethyl derivatives of arachidonic acid [66–69], HETEs [70] and leukotrienes [71,72] analogues have also been reported. Fluorine-containing natural products have also been reviewed recently [73]. Synthesis of other halogenated fatty acids was reviewed some time ago [74,75].

3. Chlorinated fatty acids

Chlorinated fatty acids have been found to be the major constituents among organohalogen compounds in fish, molluscs, and some other invertebrates and seaweed [1,5,14,19,20,22,23,76]. Chlorinated fatty acids have also been detected in high concentrations in the biota and are connected to anthropogenic inputs either directly as in the case of pulp bleaching, or indirectly formed by metabolism of other chlorinated organic compounds [5,19–21,77–80].

3.1. Chlorinated fatty acids isolated from invertebrates and fishes

More than twenty years ago White and Hager [81] reported the occurrence of chlorinated fatty acids in jellyfish (Auritia aurita, phylum Cnidaria, class Scyphozoa) lipids. Six isomeric acids, 9-chloro-10-hydroxypalmitic 23, 10-chloro-9-hydroxy-palmitic 24, 9-chloro-10-hydroxystearic 25, 10-chloro-9-hydroxystearic 26, 11-chloro-12-hydroxystearic 27, and 12-chloro-11-hydroxystearic 28, were identified for the first time from this class of invertebrates.

Reports in the last few decades indicate that chlorinated fatty acids have been found in lipids of many fish species [1,3,19–21,82–85]. Thus, 9,10-dichloro-octadecanoic acid 29, was isolated from eel lipids (Anguilla anguilla) [82], and also from jellyfish (Auritia aurita) [81]. 5,6-Dichlorotetradecanoic 30, both threo- and erythro-forms, 7,8-dichlorohexadecanoic 31, both threo- and erythro-forms, 9,10-dichlorooctadecanoic acid 29, also both threo- and erythro-forms have been identified from fish lipids by GC-ammonia positive ion chemical ionisation mass-spectrometry. Fish species, eel A. anguilla, flounder Platichthys flesus and perch Perca fluviatilis were collected along Scandinavian coast waters, the Atlantic salmon Salmo salar, in coastal area of Bothnian Sea, and Pacific salmon Oncorchynchus nerka was collected in Copper River, Alaska [85]. In the same samples and additionally from herring, acids 29–31, and 3,4-dichlorotridecanoic acid 32 were identified [3,84]. β-Oxidation of fatty acids with a shorter alkyl chain than dichlorooctadecanoic acid is assumed to take place in aquatic biota [3,84,85].
9,10,12,13-Tetrachlorooctadecanoic 33, threo-, threo- and 5,6,8,9-tetrachloro-tetradecanoic 34 acids have also been detected in fish lipids [3,86,87]. GC–MS analysis of chlorinated fatty acids was observed by Mu et al. [88]. Chlorinated fatty acids 29–32 also were found in lesser amounts in the fish lipids, grayling *Thymalus acticus*, living in central Alaska which has no direct anthropogenic influence [21].
Occurrence of chlorinated fatty acids in bivalve lipids has been reported by Wesen et al. [19]. Blue mussel *Mytilus edulis* were collected from the southern parts of the Baltic Sea, the Kattegat, the Skagerrak, and the North Sea. Among chlorinated fatty acids were found 5,6-dichoromyristic \(\text{31}\) and 7,8-dichloropalmitic \(\text{30}\) acids.

Dichlorotetradecanoic acid \(\text{31}\) was isolated from the digestive gland lipids of American lobster, *Homarus americanus* [3,89], and dichlorooctadecanoic acid \(\text{29}\) was found in lipids of pathogenic fungus *Verticillium dahliae* [90]. Two polyunsaturated fatty acids contains chlorine atom have been isolated from marine barnacle *Balanus balanoides* such as 9-chloro-8,12-dihydroxy-5,10,14,17-eicosatetraenoic \(\text{35}\) and 10-chloro-8,12-dihydroxy-5,10,14,17-eicosatetraenoic \(\text{36}\) acids [91].

3.2. Chlorinated fatty acids isolated from environments

Formation of chlorinated fatty acids and other halogenated organic compounds near industrial areas have been discussed in several review articles [1,3,20,21].

During the production of bleached paper for oxidation of lignins using elemental chlorine, chlorinated oleic and linoleic acids are the major unsaturated fatty found in the wood. Chlorinated fatty acids could be formed from these acids during wood pulp bleaching. Thus, dichlorostearic acid \(\text{29}\) has been found in bleached pulp mill effluents [92,93]. A high concentration of chlorinated fatty acids was found in eels caught in the vicinity of pulp mills [90,94].
Di-29 and tetrachlorostearic 33 acids have also been found in aquatic bottom sediments from the Gulf of Bothnia (Sweden), and around Oslo Fjords (Norway) [95]. Aquatic sediments and sewage sludges have been reported to contain considerable concentrations of organic halogens of which only a small percentage was soluble in organic solvents [96]. Many halogenated compounds, i.e. trihalomethanes, haloacetonitriles, halophenols and haloacetic acids, have been detected in the cooling effluents of three French Nuclear Power Stations to the formation of halogenated by-products. In spite of possible toxicity of such compounds towards aquatic organisms, there is an evident lack of information on the formation of halogenated compounds in chlorinated seawater samples [97].

Chlorinated fatty acids could be formed during bleaching of wheat flour, when chlorine gas or chlorine dioxide is used [98,99]. The most prominent chlorinated compounds formed in the bleaching process of flour and flour-containing food are isomers of dichlorooctadecenoic and chloro-hydroxyoctadecenoic [98,100], and also 9,10-dichlorostearic 29, 9,10,12,13-tetrachlorostearic 33, and isomers of trichloro-hydroxystearic acids [98–101].

Formation of derivatives of chlorinated fatty acids was observed during the disinfection process of drinking water [102]. The chlorine quickly incorporated into lipids by aqueous chlorination with ClO₂ and/or HOCl, to form different chlorinated acids [103]. According to Onodera et al. [104] who studied the aqueous chlorination of unsaturated fatty acids, several chloro-hydroxy-keto acids were detected. 9-Hydroxy-10-chloro-octadecanoic 23, 9,10-dichloro-12-keto-octadecanoic 37, 9,12-dihydroxy-10,13-dichlo-octadecanoic 38, and 9-keto-11-hydroxy-12-chloro-octadeca-noic 39 acids have been identified, some of which were stable in water [104].

3.3. Derivatives of chlorinated fatty acids

3.3.1. Chlorinated monocarbocyclic oxylipins

The monocarbocyclic oxylipins contain a cyclopropyl, cyclopentyl and cyclohexyl rings in the aliphatic chain and are widely common in marine organisms [105]. The marine oxylipins that contain a cyclopentyl ring, also known as prostaglandins, have been found in soft corals, sponges, some mollusc species, and in red algae [1,4,105]. A series of chlorinated prostaglandins was dis-
covered in soft corals. The striking octocoral *Telesto riisei* produced four punaglandins such as punaglandin 1—40, 2—41, 7E-punaglandin 3—42, and 7E-punaglandin 4—43 [106]. Actually punaglandins 42 and 43 exist as both the 7E- and 7Z-isomers, 44 and 45, respectively.

Similar chlorovulones I–IV (*E* - and *Z* - isomers, respectively) 46–49 produced the marine stolonifer *Clavularia viridis* [107].

Epoxy prostanoid 50 was isolated from *C. viridis* [107], and three chlorinated epoxy monocyclopentyl fatty acids, named egregiachlorine A–C 51–53, respectively, have been isolated from marine brown alga *Egregia menziesii* [108].
3.3.2. Chlorinated fatty acids incorporated in natural peptides

Chlorinated fatty acids could be incorporated into natural peptides. Thus, two novel chlorinated octanoic acids have been found to be incorporated in lyngbyabellin B 55 and dolabellin 56. These metabolites were isolated from a marine cyanobacterium, *Lyngbya majuscula*, collected near the Dry Tortugas National Park, FL, USA. This new cyclic depsipeptide displayed potent toxicity toward brine shrimp and the fungus *Candida albicans* [109]. The same chlorinated fatty acids have also been isolated from cyanobacterium, *L. majuscula* collected at Apra Harbor (Guam) by another group of researchers [110].

New chlorinated fatty acids such as 3-amino-14-chloro-2-hydroxy-4-methyl-hexadecanoic acid have been found incorporated into the natural peptides, puwainaphycin C 57 and D 58, which were isolated from cultures of the terrestrial cyanobacterium *Anabaena* sp. [111].
A series of new chlorinated peptides 60–72 has been isolated from the tropical marine sponge *Dysidea* sp. [112]. The absolute stereochemistry of the metabolites was deduced by chemical correlation with novel polychlorinated S-(−)-4,4,4-trichloro-3-methylbutanoic acid 59. Dipeptides of 62, 63, 65–69, 71–73 also contain a number of novel α-amino-chlorinated acids and their esters. A new 6,6,6-trichloro-5-methyl-2-hexenoic acid was found in the dipeptide 73 ([112] and cited references).

57. R = OH; 58. R = CH₃

67. X = Cl, R = COOCH₃
68. X = H, R = COOCH₃
69. X = Cl, R = COOH
70. X = Cl, R = CH₂OH
71. X = Cl, R = COOEt
72. X = Cl, R = COO-η-Bu

62. R = COOCH₃
63. R = COOH
64. R = CH₂OH
65. R = COOEt
66. R = COO-η-Bu
The novel and unusual polychlorinated fatty acid containing a cyclopropyl ring incorporated into the peptide periconin B has been found in the pathogenic fungus *Periconia circinata*, which causes “milo disease” of grain [113].

![Chemical structure](image)

A number of chlorinated amino acids incorporated in natural peptides and/or as the free acids in some organisms have been discovered. Thus, 2-amino-4,4-dichlorobutyric acid was the first simple naturally occurring halogenated amino acid with antibacterial properties which was identified from *Streptomyces armentosus* var. *armentosus* [114]. Another species of microbe *Streptomyces griseosporeus* produced γ-chloronorvaline [115]. 2-Amino-3-hydroxy-4-chlorobutyric acid have been found as incorporated into some cyclic peptides such as syringomycin, syringomycins E and G [116–118], syringotoxin B [118], and also syrengostatins A–H [117,119,120]. The novel amino acid have been isolated as the free acid [121] and bonded in dipeptide “FR-900148” produced by *Streptomyces viridogenes* [121], and also *Streptomyces xanthocidicus* [122,123].

Some mushrooms produced chlorinated amino acids. 2-Amino-5-chloro-4(Z)-hexenoic acid has been isolated from *Amatia solitaria* [124], and from *A. pseudoporphyria* [125,126]. The mushrooms *A. onusta* and *A. miculifera* both produced [127,128], *A. gymnopus* also produced [128]. The pseudo “White Mushroom” has the name *A. abrupta* synthesized chlorohydrin [129]. 2-Amino-5-chloro-4-pentenoic acid has been found in *A. castanopsidis* [130]. Micobiont B isolated from lichen *Xanthoria parietina* produced 2-amino-6-chloro-hexanoic acid [1].

A novel 5-chloro-α-d-tryptofan has been found after hydrolysis of the antibiotic longikatenmycin [131]. The antitumor agent U-43,895 was found in cultures of *Streptomyces svinceus* [132].

### Chlorinated fatty acids incorporated in natural alkaloids

Chlorinated fatty acids have also been found in the structures of natural alkaloids [1,5,133]. Some chlorinated pyrrolizidine alkaloids with skeleton were isolated from the plants *Senecio jacobaea* (family Compositae). The plant *S. jacobaea* named “tansy ragwort” and other *Senecio* species contains pyrrolizidine alkaloids and are dangerous to cattle and other livestock [134,135]. Chlorinated dioic (dicarboxylic) acids were present in the structures of jaconine, chlorodeoxyascelatine, doronine, and merenskine N-oxide, respectively [136–141]. 3-Chloro-2-hydroxybutanoic acid was detected in alkaloid which was isolated from *Cryptantha clevelandii* and *Cryptantha leiocarpa* (family Boraginaceae) [142].
3.3.4. Chlorinated derivatives of fatty acid amides

Fatty acid amides are widespread in nature [143]. They are incorporated into some lipid molecules such as ceramides, glycosphingolipids, N-acylated lipids, and bacterial lipoproteins [144,145]. Fatty acid amides are lipid bioregulators formed from long chain saturated and unsaturated fatty acids via amidation of the corresponding amines. Oleamides, the fatty acid ethanalamides, bind to the cannabinoid receptors of the central nervous system or peripheral tissues and can be considered as endogenous ligands of these receptors [146,147]. Their pharmacological properties were discussed [144,148].

Phytochemical investigations of *Aloe sabaea* afforded a new chlorinated amide, N-4’-chlorobutylbutyramide 94. This is the first report of the occurrence of chlorinated fatty acid amides in the *Aloaceae* family [149].

Herbamide 95, a new ketide has been isolated from the marine sponge *Dysidea herbacea* and contains the novel polychlorinated fatty acid [150].

Cyanobacteria of the genus *Lyngbya* are a rich source of bioactive secondary metabolites including fatty acid amides. A series of malyngamides 96–113 has been identified from marine cyanobacteria *L. majuscula*, including malyngamide A 96 and isomalyngamide A 97, malyngamide B 98 and isomalyngamide B 99 [151,152].
Malyngamide C 101 and its acetate 102 [153], deoxymalyngamides 100, 103 and 104 [153,154] have also been isolated from cyanobacteria *L. majuscula*. Malyngamide D 105 and its acetate 106 were detected in the same cyanobacterium from Puerto Rico collection [155]. Malyngamide G 107 produced the cyanobacterium epiphyte of the brown alga *Cystoseria crinita* [156]. Deoxymalyngamide C 103 undergoes slow conversion in chloroform at −20 °C to the indole derivative 108 [153].

Milligan et al. [157] isolated new malyngamides F 109, I 111, R 112 and Q 113 from a Madagascan cyanobacterium *L. majuscula*. Malyngamide M 110 was reported by Kan et al. [158] from the Hawaiian red alga *Gracilaria coronopifolia*. Because the malyngamides are well-known secondary metabolites of marine cyanobacteria, it has been suggested that the true producer of malyngamide M 110 is a cyanobacterium growing epiphytically on *G. coronopifolia* and on other species of *Gracilaria* [159]. Malyngamide M 110 was found in marine cyanobacterium *L. majuscula* from a Papua New Guinea collection [160].

Two new malyngamides O 114 and P 115 have been isolated from the marine hare *Stylocheilus longicauda* which was collected in Black Point, Oahu [161].

Novel fatty acid amides named stylochelamides 116 and 117 have been identified from the sea hare *S. longicauda* [162]. Mirable E 118 was isolated from cyanobacterium *Scytonema mirabile* [163].
3.3.5. Chlorinated fatty acid derivatives

The novel dichloropolyenic antibiotic enacyloxin II \( \text{119} \) has been isolated from *Gluconobacter* sp. \( [164] \). Two other dichloropolyenoic cytotoxic tetramic acid glycosides, aurantosides A \( \text{120} \) and B \( \text{121} \), have been identified from marine sponge *Theonella* sp. \( [165] \). These dichloropolyenes \( \text{120} \) and \( \text{121} \) showed good cytotoxicity in the P-388 and L-1210 assays \( [165] \).

3.4. Chlorinated carboxylic acids of marine algae

The red, brown and green marine algae, and also some microalgae from phytoplankton produced many halogenated compounds \( [166–171] \). Among them were identified a number of chlorinated carboxylic acids and their amides \( \text{122–129} \) \( [1,4,5,9,10,13] \). Thus, 2-chloroacetic acid \( \text{122} \), 2,2-dichloroacetic acid \( \text{123} \), and also chlorinated derivatives of propionic \( \text{125} \) and acrylic
Acids have been found in marine red alga *Asparagopsis taxiformis* [172]. The former alga, ‘limu kohu’ (supreme seaweed), is prized by Hawaiians for its flavor and aroma. The red alga *Marginisporum aberrans* has been found to contain dichloroacetamide [173]. Chlorinated acetic and propionic acids have been detected in fresh pine needles in concentrations up to 4 ng/g [174]. Also trichloroacetic acid was found in concentrations in the range of 2–150 ng/g in fresh needles in Finland and Central Europe [175,176], and in conifer needles [175,176]. Trichloroacetic acid concentration level has been found to be highest in summer and autumn [177–179].

### 3.5. Chlorosulfolipids

Chlorosulfolipids have been discovered in the alga *Ochromonas danica* (Chrysophyceae, Chrysophyta) where they constitute 15% of the total lipids and 3% of the dry weight of heterotrophically-grown, stationary phase cells [180,181]. Later the occurrence of a 3’-phosphoadenosine 5’-phosphosulphate synthesizing system in two *Ochromonas* species was reported [182]. Chlorosulfolipids [130–139] have also been identified from more than 30 species of both freshwater and marine algae belonging to green (Chlorophyceae), brown (Phaeophyceae), red (Rhodophyceae) macrophytic algae [183], and other microalgal species [184,185].

### 4. Brominated fatty acids

The first investigation of bromine in marine organisms was reported in the 1930s [186,187]. Significant bromine concentrations have been detected in lipid extracts from fish, molluscs, crustacea, and some marine animals collected in the Scandinavian region (Norway) [188] and Pacific Ocean (Newport and Astoria, Oregon) [189]. Lipid separation indicated that bromine was present in all fractions with the highest concentrations being associated with triglycerides, fatty acids and sterols [188]. Bromine containing secondary metabolites have also been found in many marine algae [1,4,5,9,10,13,14].
4.1. Brominated fatty acids isolated from marine algae

Red marine algae belonging to the family Bonnemaisoniaceae are a unique group that produce halogenated secondary metabolites, including some carboxylic and fatty acids [1,9,10]. Thus, the red algae *A. taxiformis* and *Asparagopsis armata* synthesize a number of brominated acetic and acrylic acids [166]. Z- and E-forms of 3-bromo-2-heptanoic acid [145] and [146], and also Z- and E-forms of 3-bromo-2-nonanoic acids [147] and [148], respectively, have been found in the red algae *Bonnemaisonia nootkana*, *Bonnemaisonia hamifera*, and *Trailliella intricata* [167]. 3,3-Dibromo-2-n-butylacrylic [149] and 3,3-dibromo-2-n-hexylacrylic [150] acids have also been isolated from *B. nootkana*, *B. hamifera*, and *T. intricata* algae species [167].

4.2. Brominated fatty acids isolated from terrestrial plants

Brominated fatty acids are rare in higher plants, and only a few of these acids were found. Two brominated stearic acids such as 9,10-dibromooctadecanoic [151] and 9,10,12,13-tetrabromooctadecanoic [152] acids were isolated from the seed oil of the Asian plant *Eremostachys molucceloides* growing in Uzbekistan [190].

Lichens are unique symbiotic organisms that produce many different halogenated compounds [4,5,191], unusual fatty acids [192–200] and betaine ether glycerolipids [201,202]. For the first
time, a series of novel brominated fatty acids have been found in some lichen species 153–160. Two new C18 acetylenic acid methyl esters of (5E,17E)-18-bromo-octadeca-5,17-diene-15-ynoic acid 153 (13.1%) and 18-bromo-octadeca-5,7,17-triynoic acid 155 (8.8%) have been isolated from the lichen Acorospora gobiensis collected in Asian Tian Shan mountains near Lake Issyk-Kul [203]. These two brominated fatty acids 153 and 155, and six other new brominated acids 154, 156–160 were found in lichens, Cladonia furcata, Lacanora fructulosa, Leptogium saturnium, Parmelia linctina, Parmelia comtseliadalis, Peltigera canina and Xanthoria sp. [204]. The methyl ester of 18-bromo-(5E,17Z)-octadeca-5,17-diene-15-ynoic acid 154 was isolated from C. furcata (0.4% of dry weight), P. linctina (2.8%), and Xanthoria sp. (5.7%) [204]. The methyl ester of 16,18-dibromo-(15E,17Z)-octadeca-15,17-diene-5,7-diynoic acid 156 was found in L. fructulosa (3.2%), P. linctina (6.3%), P. comtseliadalis (0.3%), and Xanthoria sp. (2.4%). The methyl ester of 18,18-dibromo-17-octadecene-5,7-diyonic acid 157 is present in C. furcata (3.3%), L. saturnium (1.9%), P. comtseliadalis (5.8%), and Peltigera canina (0.3%). The methyl ester of 6-bromo-(5E,15Z)-
octadeca-5,15-diene-11,13,17-triynoic acid 158 has been found in two lichen species, *P. linctina* (9.4%), *P. comtseliadalis* (3.0%). The unusual epoxy brominated fatty acid 159, 18-bromo-9-hydroxy-12,13-trans-epoxy-(10E,15Z)-octadeca-10,15-diene-17-ynoic acid, methyl ester has also been found in two lichen species *P. canina* and *L. saturnium*. The methyl ester of 18-bromo-5,6-trans-endomethylene-7,11,15-trimethyl-(8E,10Z)-octadeca-8,10-diene-17-ynoic acid 160 was found in less than 0.1 mg/50 g of dry weight [204].

Two new bromoallenic fatty acids have been found in some lichen species from Tian Shan Mountains (central Asia), (12E,15S,18S)-15-hydroxy-18-bromo-12,16,17-octadecatrienoic acid 161 and (13Z,15R,18R)-15-hydroxy-18-bromo-13,16,17-octadecatrienoic acid 162 [205].
4.3. Brominated fatty acids isolated from marine invertebrates

In the 1970s Lichfield and Morales [206,207] identified very long-chain fatty acids (C24–C28) containing the unusual 5Z and 9Z unsaturation in high proportions from marine sponges. These unusual fatty acids were named ‘demospongic’ acids. Later Djerassi discovered two new iso- and antiso-acids, i.e. 6-bromo-24-methyl-5,9-hexacosadienoic acid 166 and 6-bromo-25-methyl-5,9-hexacosadienoic acid 165 [208] from the sponges *Petrosia ficiformis* and *Petrosia hebes*. (5E,9Z)-6-Bromo-23-methyl-tetracosa-5,9-dienoic acid 163 and (5E,9Z)-6-bromo-24-methyl-pentacosa-5,9-dienoic acid 164 have been isolated from sponge *Agelas* sp. [209].

A series of 6-bromo-C20–C28 very long-chain dienoic fatty acids with 5E,9Z unsaturation 167–175 has been isolated from different species of marine invertebrates. These fatty acids usually are present in two phospholipid classes such as phosphatidylserine and/or phosphatidylthanolamine [1,2,4]. Acid 167 was detected in the marine anemone *Condylactis gigantea* (Cnidaria, Anthozoa) [210], and zoanthid *Palythoa caribaeorum* (Hexacorallina, Zoanthidea) [210]. Acids 168 and 169 were found in the anemone *Stoichactis helianthus* [211]. Acid 170 was isolated from the phosphatidylserine of the marine sponge *Siphonochalina siphonella* from Red Sea [4]. Brominated fatty acids 167–170 were present in lipids to no more 1%. Fatty acids 171–173 have been isolated from the sponges *Amphimedon terpenensis* [212,213], *Agelas* sp. [209], *Hymeniacidonid* sp. [214]. Fatty acids C27–C28 were found in the sponge *Petrozia* sp. [215], Okinawan sponge *Xestospongia* sp. [216,217], Caribbean sponge *Pseudaxinella luneachata* [2], and *Cinachyrella aff. schulzei* [218].

Some brominated highly polyunsaturated fatty acids have been isolated from marine anemone and sponges. 6-Bromo-5,9,13-docosatrienoic acid 176 was isolated from the anemone *Stoichactis helianthus* [2], and also (5E,9Z,24Z)-6-bromo-heptacosa-5,9,24-trienoic acid 177 and (5E,9Z,24Z)-6-bromo-octacosa-5,9,24-trienoic acid 178 were found in the sponges *Xestospongia* sp. [216,217]. Fatty acids 177 and 178 displayed cytotoxicity against L1210 murine leukaemia cells and KB human epidermoid carcinoma cells [217].

4.4. Biosynthesis of brominated demospongic acids

Biosynthesis of 6-bromo-Δ5,9 fatty acids with exogenous radiolabelled [1-14C] hexadecanoic acid have been demonstrated by Carballeira et al. [219]. These brominated fatty acids could
be classified in three families as: normal even-chain, normal odd-chain, and iso-odd-chain [2].

The biosynthetic pathways for normal even-chain 6-bromo-Δ^5,9 fatty acids presented in Scheme 6 was postulated by Carballeira [2]. This biosynthetic route starts with hexadecanoic acid and chain elongation up to octacosanoic acid (C28:0). Most of the longer-chain
brominated fatty acids shown, as well as the non-brominated ones, have been found in marine sponges. Typically sponges prefer brominated fatty acids between C24 and C28, although a fatty acid with C16 has also been found [216]. These postulated biosynthetic sequences take into consideration that bromine introduction occurs last, as previously shown for sponges [220].

Carballeira’s postulated fatty acid biosynthetic sequences for normal odd-chain 6-bromo-Δ⁵,⁹ fatty acids are presented in Scheme 7 [2]. The sequence probably starts with pentadecanoic acid (C15:0) and chain elongation (two carbons at a time) up to heptadecanoic acid (C27:0) have been proposed. In the normal odd-chain family brominated C23–C27 fatty acids have been isolated from sponges, and 6-bromo-Δ⁵,⁹ C21 fatty acid was found in marine anemone and Zooxanthellae [2]. Postulated biosynthetic sequences also take into consideration that bromine introduction occurs on the last biosynthetic stage [2].

4.5. Brominated polyacetylenes

Marine polyacetylenes are a large group of secondary metabolites and have been isolated mainly from sponges [1,5]. Some brominated polyacetylenic acids are derivatives of octadecanoic acid were also detected in sponges [1,4,5].

A series of 18-brominated C23 acetylenic acids 179, 181 and their ethyl esters 180, 182 have been found in the Australian sponge Phakelia carduus. They have shown positive reaction against the gram-positive bacteria Staphylococcus aureus and Micrococcus sp. [221].
Mono-, di- and tribrominated C16 fatty acids 183–188 have been isolated from sponges belonging to the family Xestospongia. Acetylenic acids 183–185 and 189 were found in Xestospongia sp. from the Red Sea [222]. (7E,13E,15Z)-14,16-Dibromohexadeca-7,13,15-trien-5-ynoic 186 was isolated from the Australian sponge Xestospongia muta [223]. 186 and also two new (7E,9E,13E,15E)-14,16-dibromohexadeca-7,9,13,15-tetraen-5-ynoic 187 and 6,14,16-tribromohexadeca-pentaenoic 188 acids have been detected in sponge Oceanapia sp. [224].
A series of brominated polyacetylenic C18 acids have been isolated from sponges living in different locations, including the Great Barrier Reef (North Australia), Red Sea (Middle East) and the Caribbean Sea (America). (9E,17E)-18-Bromo-octadeca-9,17-dien-7,15-diyne-10-oic acid was found in extracts of two sponges *Xestospongia testudinaria* and *Xestospongia* sp. (Red Sea). 18-Bromo-octadeca-17-en-5,7,15-triyne-10-oic acid and its methyl and ethyl esters were isolated from *X. testudinaria* (Pandora Reef, Townsville, Queensland, Australia). 18,18-Dibromo diacetylenic acid and its methyl ester were isolated from *Xestospongia* sp. (Red Sea). Brominated fatty acids and their esters have good antibacterial activity against *S. aureus* and *Bacillus subtilis*. Brominated acids from *X. muta* have been shown to inhibit HIV protease, a critical enzyme in the replication of human immunodeficiency virus.
Marine sponges belonging to the families *Nepheliospongia* and *Haploscleria* produce many different acetylenic metabolites including polyacetylenes [4,5,230–235], acetylenic glycerol ethers [236,237]. A novel series of brominated C18 tri-196–208 and diacetylenic 209–212 fatty acids has been isolated from the sponge *Petrosia volkano* (Japan Sea) [238]. All isolated polyacetylenic acids have anti fungal activity against pathogenic fungus *Mortierella ramannianus* [238].

4.6. Brominated monocarbocyclic oxylipins

The chlorinated monocarbocyclic oxylipins containing a cyclopentyl ring in the aliphatic chain, well known also as prostaglandins, have been found in soft corals, sponges, some mollusc species, and in red algae 40–53 [1,4,105]. Only one brominated prostaglanoid named bromovulone 1 213 has been found in the stolonifer *Clavularia viridis* [239].
4.7. Brominated amides of carboxylic acids

The marine sponge *Clathria* sp. produces brominated fatty acid amides: clathrynamides A 214, B 215, and C 216 [240]. These identified metabolites are potent inhibitors of cell division of starfish eggs (IC\textsubscript{50} = 6 ng/ml) and also are cytotoxic towards K-562 human myeloid cells (IC\textsubscript{50} = 0.2 \(\mu\)g/ml) [240].

![Chemical structures of clathrynamides A, B, and C.](image)

The calyculins, unique polyketides bearing nitrogen and phosphorus functions, have been isolated from the Japanese marine sponge *Discoderma calyx* [241 and cited references], but only calyculin J 217 contains bromine [241]. Brominated tyrosine derivatives include lipopurealin A 218 was detected in *Psammaplysilla purea* [239]. Alternatamide B, bromotryptamine amide 219, has been found in extract of the Atlantic *Amathia alternata* [239]. The novel brominated dipeptide bromotetaine 220 was isolated from *B. subtilis* [239].

4.8. Brominated fatty acid derivatives

The Australian marine cyanobacteria *Lyngbya* sp. produced the brominated ester of 2,5-dimethyl-dodecanoic acid 221 [242]. Bromoester 222 was detected in the cerebrospinal fluid of a normal human [5]. A collection of *Lyngbya majuscula* from Grenada produced the cyclopropyl-containing fatty acid metabolites grenadadiene 223, which gave an interesting cytotoxicity profile in the NCL 60 cell line assay, the debrominated analogues nadadiene 224 showed modest cannabinoid receptor binding activity [241]. Also detected compound 221 [243]. Another unusual brominated metabolite named \(4(E)-S\)-antazirine 225 has been isolated from the Pohnpei sponge *Dysidea fragilis* [244]. Oscillariolide 226 a brominated macrolide has been isolated from the cyanobacterium *Oscillatoria* sp. [239]. The iso-butyl ester of the unusual fatty acid xanthomonadin I 227 is produced by the walnut pathogen *Xanthomonas juglandis* [239].
4.9. Brominated amino acids incorporated in natural peptides

A few brominated amino acids have been found in the structures of natural peptides [5,14,22,23,239,245]. Thus, in particular the 6-bromotryptophan unit appears in several sponge metabolites, such as celenamide E 228 from the Patagonian sponge *Cliona chilensis* [246], and cyclocinamide A 229 from *Psammocinia* sp. Some 2-bromo-tryptophan metabolites, such as jaspamide 230 isolated from several sponges, are also known [239]. Several bromotyrosine and bromophenylalanine cyclic peptides are known from sponge sources. Geodiamolide I 231 was found in the sponge *Geodia* sp. and the cyclic peptide theopalauamide 232 (a partial structure of the peptide is shown) was produced by filamentous bacteria associated with the lithistid sponge *Theonella swinhoei* [247]. Many different brominated tyrosine derivatives isolated from marine sponges [5,239,245] are not included in this review.
5. Iodinated fatty acids

Natural iodinated fatty acids are much rarer than the chlorinated and/or brominated acids. Simple iodinated acetic 233, 234 and acrylic acids 235, 237, 239 and their ethyl esters 236, 238, 240 have been isolated from the marine red algae Asparagopsis taxiformis [16,166,172] and Aaparagopsis armata [166].

The formation of iodolipids in thyroid tissue has been known for a long time, but the chemical structures as well as their physiological role remained unclear. Iodolipids in calf thyroid slices were characterized as iodinated free fatty acids and neutral lipids [248,249]. Suppression of iodine organification as well as phospholipase A2 strongly decreased their formation, whereas inhibition of prostaglandin synthesis increased lipid iodination, suggesting a correlation to the arachidonic acid metabolism [250]. Transformation of arachidonic and docosahexaenoic acids by the action of lactoperoxidase, iodine and hydrogen peroxide into iodolactones has been demonstrated in vivo [250,251]. Lactoperoxidase catalyzes the transformation of 5,8,11,14-eicosatetraenoic and 4,7,10,13,16,19-docosahexaenoic acids to iodolactones. Major lactones formed in this reaction are: δ-lactone of 6-iodo-4-hydroxy-eicosa-8,11,14-trienoic acid 241, and ε-lactone of 5-iodo-4-hydroxy-docos-7,10,13,16,19-pentaenoic acid 242 [248,249].

Also two other ω-lactones 243 and 244 have been detected by GC–MS [248,249,252]. The formation of the ω-lactone of 14-iodo-15-hydroxy-eicosa-5,8,11-trienoic acid 243 and the ω-lactone of 15-iodo-14-hydroxy-eicosa-5,8,11-trienoic acid 244 is shown in Scheme 8. Pereira et al. [253] have been demonstrated the formation of iodolipids by incorporation of iodine into proteins and lipids of horse thyroid slices. The authors have identified the major thyroid iodolipid to be 2-iodo-hexadecanal. The biosynthesis of the iodolipid is likely to involve the addition of iodine to the vinyl ether group of plasmeneylethanolamine, which is the main
thyroid phospholipid (Scheme 9). 2-Iodo-hexadecanal has also been found as the major iodolipid in dog and rat thyroid [253].

5.1. Iodinated amino acid derivatives

Although iodinated tyrosines have been known for more than 100 years ever since 3,5-diiodotyrosine 246 named as ‘iodogorgoic acid’ was first isolated from the marine gordonian Gorgonia cavolinii [254–256], iodine much less frequently than chlorine and/or bromine is incorporated into natural compounds [4,5,14]. The first report of the isolation of thyroxine 247 from mammalian thyroid gland was published in 1915 [257], followed by later publications [258,259]. Thyroxine
and other iodinated tyrosines 248–250 have been isolated from numerous ascidians, sponges, gorgonians, marine algae and insects, see reviews [5,14,239]. 2-(or 4)-Iodohistidine 251 has been found in several insects such as the squash bug, house fly, mosquito, dragobfly, and cockroach [260]. Iodinated phenethylamine compounds and urea derivative 252 were isolated from marine tunicate [261].

Scheme 9. The proposed biosynthesis of 245 by the addition of iodine (I⁺) to the vinyl ether of plasmalogens followed by the cleavage of the O-1-alk-1'-enyl bond (Adapted by authors).
5.2. Iodinated amino acids incorporated in natural peptides

A series of cytotoxic peptides 253–256 containing iodinated amino acids have been isolated from some marine sponges. Thus, geodiamolides G 253 and 255 were identified from the Papua New Guinea sponge Cymbastela sp. [262]. The closely related geodiamolide A 254 [263] was found in the Caribbean species of sponges Geodia [263], and Papua New Guinea sponge Pseudaxinyssa sp. [264]. Talpir et al. [265] identified the geodiamolide TA 256 from the South African sponge Hemiasterella minor. Geodiamolides G 253 showed activity against glioblastoma, astrocytoma U 373, and human ovarian carcinoma HEY [262].

6. Polyhalogenated fatty acids

Some marine algae produce many organohalogens [5,9,10]. Thus, the Hawaiian alga A. taxiiformis, the Mediterranean A. armata, and red alga Falkenbergia rufolanosa synthesize more than 100 different halogenated compounds, including polyhalogenated carboxylic acids, their esters and amines 257–263 [9,10,166,167,169–172].

Recently, Rezanka and Dembitsky [266] identified some polyhalogenated homosesquiterpenic fatty acids 264–266, and also chlorinated fatty acid 267 from the red alga Plocamium cartilagineum.
7. Biohalogenation

The enzymatic halogenation of different organic substrates accompanies formation of the corresponding halogenated compounds. Haloperoxidases are a group of enzymes that are able to catalyse the halogenation of organic compounds in the presence of halide ions and peroxides such as $\text{H}_2\text{O}_2$. These enzymes have received increasing interest due to their ability to halogenate a range of organic compounds of both commercial and pharmaceutical interest. Many natural products such as brominated acetylenic acids, or halogenated indoles have potent anti-inflammatory and anticancer activities. Also haloperoxidases have been shown to carry out epoxidation, sulfoxidation, and oxidation of different of both natural and synthetic compounds. Haloperoxidases have been isolated from lichens, fungus, marine algae and invertebrates, animals, and also some microorganisms. Since many reviews on various aspects of biohalogenation are available [267–275], the discussion of their mechanisms will be limited here.

7.1. Chloroperoxidase

Chloroperoxidase occupies a unique niche among hemeprotein enzymes [276]. The marine fungus *Caldariomyces fumago* is an excellent source of chloroperoxidase and its biological chlorination ability has been proved extensively in variety of substrates such as: fulvic, cinnamic and barbituric acids, $\beta$-keto acids, alkenes and alkynes, thiols, cyclopropanes, 1,3-diones, tyrosine, anisoles, thiazole, nitrogen heterocycles, phenols and anthraquinones [277–292]. Chloroperoxidases have also been isolated from the bacterium *Pseudomonas pyrocinia* [293–295], the terrestrial fungus *Culvularia inaedualis* [296,297], the acorn worm *Notomasrus lobatus* [298], and also are present in the mycelium of the white-rot fungus *P. chrysosporium* [299], the white-rot fungus
Trametes versicolor [300]. Recently, the structures of chloroperoxidases from Streptomyces aureofaciens [301], Streptomyces lividans and Pseudomonas fluorescens [302] have been studied. Some examples of the activity of chloroperoxidases are shown in Scheme 10.

7.2. Bromoperoxidase

Bromoperoxidases have been discovered from many algal species. Thus, Hewson and Hager [303] in 1980 reported a survey of the bromoperoxidase activity in 72 species of marine algae. Recently Moore and Okuda [304] reexamined and studied 94 species of marine red, brown, and green algae from a wide range of geographical and environmental habitats for presence of bromoperoxidases. According to this study [304], the authors found that bromoperoxidase activity was prevalent in the red and green algae. The presence of bromoperoxidase in an individual alga species does not always correlate with presence of halogenated natural compounds, thus suggesting an alternative role for these enzymes in nature, and in particular, in algae species.

Bromoperoxidases have also been found in the lichen Xanthoria parientina [305]. Bromoperoxidase activity and brominated fatty acids 153 and 155 were identified from lichen Acorospora gobiensis [203]. Bromoperoxidases have been isolated from some bacteria such as Streptomyces phaerocromogenes [306,307], S. aureofaciens [308–311], S. griseus [312], S. venezuelae [313]. The strains Pseudomonas pyrrocinia [314], P. aureofaciens, P. putida, P. pyrohinitrica, and P. aeruginosa [315,316] all possess one or more bromoperoxidases.

The marine annelid Thelepus setosus and the acorn worm Ptychodera flava laysanica, both produced bromoperoxidase [317].

Some examples of the action bromoperoxidase are shown in Scheme 11.

Scheme 10. Representative reactions catalyzed by chloroperoxidase.
8. Addition to halogenated fatty acid analogues and derivatives

Chlorinated fatty acid amides such as gymnastatins A–E \(268-280\) and their derivatives have been isolated from a strain of \textit{Gymnascella dankaliensis} originally separated from the sponge \textit{Halichondria japonica}. Gymnastatins A–C \(268, 271\) and \(272\) exhibited significant cytotoxicity against cultured P388 cells [318]. Previously, Numata et al. [319] reported the presence of gymnastatins A–C \(268, 271\) and \(272\) in the fungal strain of \textit{G. dankaliensis}. Also gymnastatins A–C \(268, 271\) and \(272\), showed significant cytotoxicity against tumour cell lines [319].

Pitiamide A \(275\), a new chlorolipid has been isolated from a mixed collection of \textit{L. majuscula} and a \textit{Microcoleus} sp. growing on hard coral \textit{Porites cylindrica} in Guam [320].

Halogenated fatty acids containing heterocycle derivatives are rare in nature. However a few natural compounds have been found in some organisms.

A series of brominated pyrrol acid derivatives \(276-285\) has been detected mainly in marine sponges. One of first such metabolites was oroidin \(282\) isolated from the \textit{Agelas oroides} from the Bay of Naples [321]. Sponge \textit{A. flabelliformis} from the Bagamas produced some simple pyroles \(276-280\), and these compounds exhibited potent immunosuppressive activity [322]. From another \textit{Agelas} sponge, 2,3-dibromopyrrole acid \(279\), and its methyl ester \(280\) was isolated [323]. Several amide derivatives \(281, 283-285\) have been isolated from sponges also belonging to genus \textit{Agelas}: \(281\) from \textit{Agelas} sp. [324], \(283, 284\) from \textit{A. mauritiana} [325], and keramadine \(285\) from Okinawan \textit{Agelas} sponge [324]. Keramadine \(285\) is a novel antagonist of serotonergic receptors [326].

Thus, thiazohalostain \(286\) which has a cytoprotective effect and prevents cell death caused by calcium overload was isolated from a culture of \textit{Actinomadura} sp. [327,328], and the methyl ester of sulfuric acid named as mauritamide A \(287\) was found in the Fijian sponge \textit{Agelas mauritiana} [329]. Manzacidin A \(288\), B \(289\), and C \(290\) were isolated from Okinawan \textit{Hymeniacidon} sp. sponge [330].

6-Chloroindoleacetic acid derivatives \(291, 292\) were discovered in the seeds of some terrestrial plants belonging to family Leguminosae: \textit{Lathyrus latifolius} [331], \textit{L. maritimus} (sea pea), \textit{L. odoratus} (sweet pea), \textit{L. sativus} (grasspea), \textit{Lens culinaris} (lentil) [332], \textit{Pinus sylvestris} (Pinaceae)
Pisum sativum (green peas) [331,334,335], Vicia faba (fava bean) [335–337], and V. amurenensis [338]. Also P. sativum contained (S)-4-chlorotryptophan 293 in the protein of the seeds [339,340], as well as the malonyl derivatives 294, 295 [340].

6-Bromoindole derivatives 294–300 were detected in marine sponges. Thus, metabolites 294–297 were identified from the deep-water sponge Pseudosuberites hyalinus [341], and 295 was isolated from the sponge Pleroma menoui from the Coral Sea [342]. The Okinawan sponge Penares sp. produced bromoindoleacrylic acid 298 [343], and from the sponge Iotrochota sp. the indoleacrylate 299 was isolated [344]. In the sponge Corallistes undulatus analogues of indoleacrylate 299 with Z-double bond were found [345].
Two isomers of L-6-bromohypaphorine 301 and 302 have been isolated from the sponge *Pachymatisma johnstoni* [346], and *Aplysia* sp. [347], respectively.

6-Bromoindole sulfuric acid derivatives 303–306 were found in some mollusc species: compounds 303 and 304 were found in *Murex trunculus*, *M. brandis*, *M. erinaceus*, and *Purpura haemastoma* [348], and 305 and 306 were isolated from *Dicathais orbita* [349].

The fungus *Monilinia fructicola* produces two chloromonilicin acids A 307 and B 308 [350]. Strobilurin B 309 was isolated from fungus *Strobilurus tenacellus* and *Mycena* sp. [351].

Derivatives of the 3-chloro-2-methyl-2-hydroxybutanoic acid, named as peucharin 310, peucharinin 311, and peucharinidin 312 have been isolated from roots of plant *Peucedanum arenarium* (Umbelliferae) [352].

Five new halogenated prostanoids 313, 314, 316–318 were isolated from the Okinawan soft coral *Clavularia viridis* [353]. Iodoprostanoid 313 demonstrated cytotoxic activity. Iodoprostanoinds 31–325 were obtained by chemical conversion of 313.

301

302

303. \( R = H \)

304. \( R = \text{SO}_3\text{CH}_3 \)

305. \( M = \text{CH}_3\text{NCH}_2\text{CH}_2\text{OH} \)

306. \( M = \text{CH}_3\text{NCH}_2\text{CH}_2\text{OCOCH}=\text{CCH} \)

307. \( R = \text{OH} \)

308. \( R = \text{H} \)

309

310. \( R = \text{OCOC(CH)}_3 \) \( \text{CH}_3\text{CH} \)

311. \( R = \text{OCOC(CH)}_3\text{OHCH}(\text{Cl})\text{CH} \)

312. \( R = \text{COC} \) \( \text{CH}_3\text{CH}_3 \)
9. Biological significance

The biological significance of natural fatty acids has been described in many reviews and summarized recently [354] and, therefore, has not been discussed in this review. More interesting is the possible biological significance of halogenated fatty acids. First, is the question of interest to biologists, chemists and biochemists as to why organisms synthesize many different halogenated fatty acids and their analogues and derivatives? This question does not have a simple explanation.

Natural halogenated fatty acids and also other halometabolites are produced by the action of haloperoxidases. Biohalogenation is characterized by wide substrate specificity. A variety of organic functionalities that are nucleophilic can be halogen acceptors, in particular \( \alpha,\beta \)-unsaturated acids, \( \beta \)-keto acids, alkenes and alkynes. Mechanisms and products of these reactions are diverse, but of apparent relevance to halogenated fatty acid biosynthesis are well-known pathways via interhalogen or hypolalous acid addition to unsaturation sites followed by molecular rearrangements or subsequent reactions. In recent years, halogenated peroxidases (chloro- and bromo-) and other natural enzymes have been detected and isolated from many marine algae [267,270,303], and some terrestrial plants [203,267,305]. It is reasonable to assume that these peroxidases promote synthesis of halogenated compounds, and thus provide a natural origin for the production of halogenated metabolites.

The presence of halogen atoms (F, Cl, Br or I) in the fatty alkyl chain causes significant changes in the physico-chemical characteristics of fatty acids, increasing their reactivity and changing the conformation of biological membranes.

The introduction, for instance, of a fluorine atom into the double bond of natural products has been of great interest because the fluorinated analogues of natural compounds, particularly fatty
acids are expected to have pharmacological properties different from those of the original products.

A number of careful investigations have provided strong evidence for the role that particular halogen-containing compounds serve in their natural setting [355,356]. Recent studies have indicated a chemical defensive role for halogen-containing metabolites in many marine invertebrates [357–364]. Thus, many mollusca species have a passive life-cycle and produce different unusual compounds such as 6-bromoindole sulfuric acid derivatives 303–306 which are toxic to active animals, including fish, starfish, etc. Many compounds can be quite toxic to potential predators or harmful bacteria since marine invertebrates lack the mobility enjoyed by fish. Also marine algae produce many halogenated carboxylic acids 122–129, 140–150, 233–238, many of which have antimicrobial activity. The presence of these compounds prevents algae being eaten by active molluscs, crustaceans, and/or fishes.

Fluoroacetate and fluorinated fatty acids 3–14 were identified from plants belonging to the genus *Dichapetalum* growing in South Africa, or the Australian plants *Acacia* growing in Queensland, e.g. in counties with hot and dry climates. We do not know why these plants produce these metabolites, but at present it is known that some organohalogens are insect antifeedants [363,364].

Why chlorinated fatty acids 23–36, are accumulated among halogenated compounds in fish, molluscs, invertebrates and seaweed is likewise not easily answered. Chlorinated fatty acids were detected in high concentrations in the biota and are connected to anthropogenic inputs either directly as in the case of pulp bleaching, however, many chloro-containing metabolites are produced naturally by some terrestrial plants. Some are biologically active, for example, 4-chloro-3-indoleacetic acid 291 which is a natural plant growth hormone in peas and in some types of beans. Also many different biologically active compounds such as chlorinated monocarbocyclic oxylipins 40–53 or fatty acid amides 96–99, 109–118, 269–275 were found in invertebrates where anthropogenic influence does not occur [366].

Also interesting is the question concerning halogenated fatty acids incorporated into structures of natural peptides 55–74, 228–232, 253–256 and/or natural alkaloids 98–93 found in cyanobacteria, marine invertebrates, and terrestrial plants, or free halogenated amino acids 75–87 found in some fungi, and microorganisms. We are quite certain that the synthesis of halogenated peptides and/or alkaloids by organisms does not involve chlorine, bromine, or iodine from anthropogenic sources.

The unusual chlorosulfolipids 130–139 occur in the alga *Ochromonas* and in more than 30 species of both freshwater and marine algae. These lipids are synthesized by algae for supporting mesomorphic membrane states and are utilized by algae living in extreme environmental conditions [180,181,365].

Many brominated fatty acids 163–212 which are found mainly in marine sponge species, collected in different regions of oceans, have taxonomical significance [1,2,4].

10. Concluding remarks

Novel natural halogenated fatty acids and also their analogues and derivatives have been discovered and evaluated for their biological activity. It seems certain that some possess anticancer,
antifungal and/or antibacterial properties. Certainly other important fatty acids derivatives possessing biological activity also will be discovered. Halogens play an important role in natural processes, both biogenic and abiogenic, and only by an improved understanding of the processes of biological halogenations can new information about biological significance of halogenated fatty acids and other organohalogen compounds be evaluated.

At the present time more than 3000 naturally halogen-containing metabolites have been isolated from living organisms. However, it is still not known whether these compounds are produced by environment factors [3,20,21,77–89].

References


