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Naturally occurring organoiodines

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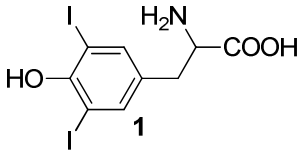
Abstract –The review, with 290 references, presented the fascinating area of iodinated natural products over the past hundred years for the first time, covered literatures published in 1896 to 2014, referring to compounds isolated from biogenic and abiotic sources. Total 182 naturally occurring organoiodine compounds were recorded. The emphasis was on compounds together with the relevant biological activities, sources, collection places, country of origin, biosynthetic studies, and first total syntheses.

Content

1 Introduction

Professor Gordon W Gribble has written many excellent comprehensive reviews on naturally occurring organohalogens,[1-8] most of them have focused on naturally occurring organochlorines,[9] organobromines,[10, 11] and organofluorines,[12] so far no review especially focus on natural organoiodines. The first reported, naturally occurring iodinated organic compound, 3,5-diiodotyrosine (DIT, **1**), was isolated in 1896 from the coral *Gorgonia cavolinii*.[13] Although DIT named as 'iodogorgoic acid' has been known for more than 100 years,[13-15] iodine was much less frequently than chlorine and/or bromine incorporated into natural compounds.[2] Currently there were over 5000 halogenated natural products known, from bacteria, fungi, algae, plants, animals, and humans.[8] Chlorometabolites and bromometabolites[11, 16] were predominate, while fluorinated natural products[17, 18] were much less common, organoiodines were rarely found in nature.[5] Herein, we try to describe all natural organoiodines and relevant halogenases in this review.



1

2 Biogenic sources

2.1. Marine organisms

Marine natural products tend to incorporate halogens more frequently than secondary metabolites from terrestrial sources.[19] The incorporation of bromine or chlorine was by far the most common, with iodine rare and fluorine extremely rare,[20] and this may be considered, to some extent, a consequence of the relatively low abundance of iodine in seawater (almost one thousand times less than bromine).[21]

2.1.1. Algae

The widely used organic chemical reagent, iodomethane (CH_3I, **2**), has a large biogenic source in worldwide marine algae, which was often detected in emissions from algae.[22-42] It was produced by the marine algae *Pavlova gyrans*, *Papenfusiella kuromo*, *Sargassum horneri* (Mikuni, Fukui Prefecture; Uozu, Toyama Prefecture; and Tsugaru Channel, Eyama, Hokkaido, Japan, respectively). Methyl halides were synthesized from *S*-adenosyl-1-methionine in cell-free extracts of *P. gyrans*, *P. Kuromo*, and *S. horneri*. This mechanism corresponds to the emission of methyl halides from the three algae *in vivo*.[25] **2** was also produced by the marine algae *Macrocystis pyrifera*,[43] *Asparagopsis taxiformis*,[44, 45] *A. armata*,[46] and Fucales *Sargassum* sp.[1, 3, 8, 47] Marine algae produces an array of both simple and complex organohalogens, presumably for chemical defense. Laboratory cultures of marine phytoplankton also produced **2**.[23] Diiodomethane (CH_2I_2, **3**) also has numerous marine algae sources,[22, 29, 31, 35-42, 48-53] but iodoform (CHI_3, **4**) has been found only in *Asparagopsis taxiformis*, which was an edible red alga that was highly favored in Hawaii for its strong aroma and flavor. *A. taxiformis* was rich in iodine, but free molecular iodine was not present in the live algae plants. The essential oils were composed of mainly bromine- and iodine-containing haloforms,[45] and small to trace

amounts of many other halogenated compounds, CH_2I_2 **3**, CHI_3 **4**,[44] dibromoiodomethane ($CHBr_2I$, **5**),[2] bromodiidomethane ($CHBrI_2$, **6**),[45] bromochloroidomethane (CHBrClI, **7**),[45] bromoiodomethane (CH_2BrI, **8**),[2] carbonyl iodide (COI_2, **9**),[44] 2-iodoethanol (ICH_2CH_2OH, **10**),[44] 1-bromo-2-iodoethane ($BrCH_2CH_2I$, **11**),[2, 54] iodoacetone (CH_3COCH_2I, **12**),[44] 1-bromo-3-iodo-2-propanone ($BrCH_2COCH_2I$, **13**),[44] 1,1-dibromo-3-iodo-2-propanone ($ICH_2COCHBr_2$, **14**),[44, 46] 1,3,3-tribromo-1-iodo-1-propene ($BrIC{=}CHCHBr_2$, **15**),[44, 45] and 1-iodo-4,4-dibromo-3-buten-2-one ($Br_2C{=}CHCOCH_2I$, **16**).[44, 46] Related nonvolatile compounds bromoiodoacetamide ($BrICHCONH_2$, **17**),[55] diiodoacetamide ($I_2CHCONH_2$, **18**),[55] bromoiodoacetic acid (BrICHCOOH, **19**),[56, 57] and diiodoacetic acid ($I_2CHCOOH$, **20**)[55] were present in the methylene chloride[55] and aqueous extracts of the lyophilized marine algae. Interestingly, none of these iodinated compounds existed in the asexual *Falkenbergia rufolanosa.* The red alga *Bonnemaisonia hamifera* (Baja California, USA) indicated high lipid bromine and iodine content (3,3-dibromo-1-iodo-2-heptanone, $CH_3CH_2CH_2CH_2CBr_2COCH_2I$, **21**),[58] high antimicrobial activity against *Bacillus subtilis*, and a remarkably persistent, sweet odor associated with the wet alga.[58] Marine algae were rich source of iodoethane (CH_3CH_2I, **22**),[22, 31, 35, 37, 42, 48, 49, 59] 1-iodopropane ($CH_3CH_2CH_2I$, **23**),[22, 31, 36, 39, 42, 59] 2-iodopropane (CH_3CH_3CHI, **24**),[22, 31, 39, 42, 59, 60] and iodobutane ($CH_3CH_2CH_2CH_2I$, **25**).[61] Iodoacetic acid (ICH_2COOH, **26**),[55, 57] 3-iodo-2-propenoic acid (ICH=CHCOOH, **27**),[57] 3,3-diiodoacrylic acid ($I_2C{=}CHCOOH$, **29**),[57] 2,3-diiodo-2-propenoic acid (ICHCICOOH, **31**),[57] and their ethyl esters (**28**, **30**, and **32**), have been isolated from the marine red algae *Asparagopsis taxiformis* (Hawaii, USA)[46, 57] and *A. armata* (Gulf of California, USA).[46] The red algae *A. taxiformis*, *A. armata*, and *Falkenbergia rufolanosa* synthesized more than 100 different

halogenated compounds, including bromoiodoacetacetic acid ethyl ester ($BrCHICOOCH_2CH_3$, **33**),[56, 57] chloroiodoacetamide ($ClCHICONH_2$, **34**),[55] 2,3-dibromo-3-iodo-propenoic acid (BrIC=CBrCOOH, **35**),[45, 46, 55, 57, 62-65] chloroiodomethane (CH_2ClI, **36**),[2] 1-bromo-1-chloro-3-iodo-2-propanol ($ICH_2CHOHCHBrCl$, **37**),[55] 1-bromo-3-iodo-2-propanol ($BrCH_2CHOHCH_2I$, **38**),[55] chloroiodoacetic acid ($ClCHICOOH$, **39**),[57] 1-chloro-3-iodo-2-propanol ($ICH_2CHOHCH_2Cl$, **40**),[55, 66] 1-chloro-3-iodoacetone ($ClCH_2COCH_2I$, **41**),[46] 1,1-dibromo-3,3-diiodo-2-propanol ($I_2CHCHOHCHBr_2$, **42**),[55] 1,1-dibromo-3-iodo-2-heptanone ($H_3C(CH_2)_3CHICOCHBr_2$, **43**),[67] 1,1-dibromo-3-iodo-2-propanol ($ICH_2CHOHCHBr_2$, **44**),[55] 2,3-dibromo-3-iodo-2-propenoic acid (BrIC=CBrCOOH, **45**),[57] 3,3-dibromo-2-iodo-2-propenoic acid ($Br_2C=CICOOH$, **46**),[57] 1,3-diiodo-2-propanol ($ICH_2CHOHCH_2I$, **47**),[55] 2,3-diiodoacrylic acid ($ICHCICOOH$, **48**),[57] iodoacetamide (ICH_2CONH_2, **49**),[55, 57] 3-iodohexadecanoic acid methyl ester ($CH_3(CH_2)_{12}CHICH_2COOCH_3$, **50**),[68] 1-iodopentane ($CH_3CH_2CH_2CH_2CH_2I$, **51**),[69] 1,1,3-tribromo-3-iodo-2-propanol ($Br_2CHCHOHCHBrI$, **52**),[55] and triiodoacetaldehyde (I_3CCHO, **53**).[70] The red alga *Delisea fimbriata* produced 1,1-dibromo-2-iodo-1-octen-3-one ($H_3C(CH_2)_4COI=CBr_2$, **54**) and 1,1-dibromo-4-chloro-2-iodo-1-octen-3-one ($CH_3(CH_2)_3CHClCOICBr$, **55**), which showed mild antifungal activity.[71] An unusual nucleoside, 4-amino-7-(5'-deoxy-*β*-*D*-xylofuranosyl)-5-iodopyrrolo[2,3-d]pyrimidine (**56**) was isolated from the alga *Hypnea valendiae*,[72] it was found to cause complete inhibition of cell division in fertilized sea urchin eggs at a concentration of 1 μg/mL and showed weak activity against human colorectal cancer cells (HCT116) with an IC_{50} >20 ppm.[73, 74] Aromatic sesquiterpene **57** was isolated from the organic extracts of North

Aegean Sea *Laurencia microcladia* (Vroulidia Bay, Chios Island, Greece). The cytotoxicity of **57** was evaluated against five human tumor cell lines (HT29, MCF7, PC3, HeLa, and A431), the IC_{50} values were 78.4, 86.3, 88.5, 81.4, and 92.7 μM, respectively.[75] Polar constituent 2,3,5,6-tetroiodo-tyrosine **58** was isolated from the green alga *Cladophora densa* Harvey (Mukoujina Reef, Hiroshima Bay, Japan).[76]

A methanol extract of the red alga *Hypnea valendiae* (Quobba Lagoon, Australia), produced pronounced muscle relaxation and hypothermia in mice and also blocked polysynaptic and monosynaptic reflexes.[72]

4-amino-7-(5'-deoxyribos-1'β-yl)-5-iodopyrrolo[2,3-d]pyrimidin (5'-deoxy-5-iodotubercidin, **59**) and its 1′ α isomer **60** have been isolated from the alga. Starting with 5-iodotubercidin **61** (IC_{50} = 0.026 μM)[77] as lead inhibitors of the isolated human AK, a variety of pyrrolo[2,3-d]pyrimidine nucleoside analogues were designed and prepared by coupling 5-substituted-4-chloropyrrolo[2,3-d]pyrimidine bases with ribose analogues using the sodium salt-mediated glycosylation procedure. 5'-Amino-5'-deoxy analogues of 5-bromo- and 5-iodotubercidins were found to be the most potent adenosine kinase inhibitors (AKIs) reported up to date (IC_{50} < 0.001 μM). Several potent AKIs were shown to exhibit anticonvulsant activity in the rat maximal electric shock induced seizure assay.[78] 5-Iodotubercidin (**61**) increased fatty acid oxidation activity of the liver at the expense of lipogenesis, the effect on fatty acid metabolism was mediated by the inhibition of acetyl-CoA carboxylase, probably due to more than twice increased in the AMP/ATP ratio and the concomitant stimulation of the AMP-activated protein kinase.[79] 5-Iodotubercidin (**61**) blocked β(3) phosphorylation without affecting the efficacy of calyculin A to inhibit platelet aggregation and spreading.[80] Tumor suppressor p53, which is activated by various stress and oncogene activation, is a target for anti-cancer drug development.

5-Iodotubercidin is a strong p53 activator. 5-Iodotubercidin (**61**) is purine derivative and is used as an inhibitor for various kinases including adenosine kinase. 5-Iodotubercidin could cause DNA damage, verified by induction of DNA breaks and nuclear foci positive for γH2AX and TopBP1, activation of Atm and Chk2, and S15 phosphorylation and up-regulation of p53. 5-Iodotubercidin induces G2 cell cycle arrest in a p53-dependent manner. It also induces cell death in p53-dependent and -independent manners. DNA breaks were likely generated by incorporation of 5-Iodotubercidin metabolite into DNA. Moreover, 5-Iodotubercidin showed anti-tumor activity as it could reduce the tumor size in carcinoma xenograft mouse models in p53-dependent and -independent manners. 5-Iodotubercidin is a novel genotoxic drug that has chemotherapeutic potential.[81] An unusual 3-iodo-*δ*-lactone (**62**) was isolated from the ethyl acetate extract of South China Sea alga *Laurencia majuscule* (Xisha Islands, Hainan Province, China), the extract showed that phytohormone-like and antifungal activities against *Sclerotinia sclerotiorum*.[82] Eiseniaiodides A (**63**) and B (**64**) were isolated from the brown alga *Eisenia bicyclis* (Johgashima Island, Kanagawa Prefecture, Japan), they were ecklonialactone derivatives containing an iodine atom.[83] Two iodobromo-aromatic sesquiterpenes, 10-bromo-7-hydroxy-11-iodolaurene (**65**) and iodoether A (**66**), were isolated from the red alga *Laurencia nana* Howe (Isla Mujeres, Mexico).[84] The peracetylated ethanolic extract of the brown alga *Carpophyllum angustifolium* (Panetiki Island, Cape Rodney, New Zealand) has furnished 2[D′]iododiphlorethol (**67**),[85, 86] which was reisolated from an ethyl acetate fraction of the brown alga *Cystophora retroflexa*.[86] Interestingly, Shibata *et al.*[87] have found that the Laminariales *Eisenia bicyclis* and *Ecklonia kurome* (Itoshima Peninsula, Fukuoka Prefecture, Japan) released dibromo-iodophenol (**68**) in the surrounding medium, and retained oligomers and

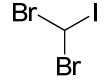
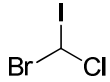
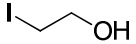
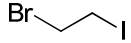
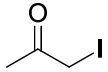
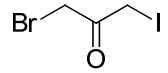
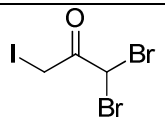
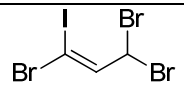
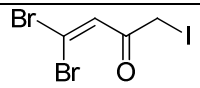
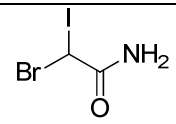
polymers in their tissues. It was found as the UV-absorbing substance, would seem to act as a chemical defence agent of brown algae against environmental stresses, such as herbivore or pathogen attack. Iodophloroeckol (**69**) and 4′-iodoeckol (**70**) were isolated and have been identified in the Laminariale *Eisenia arborea* Areschoug (Bamfield, Canada).[88] These phenols were synthesized by directed *ortho*-lithiation and *ipso*-iododesilylation reactions of *O*-aryl *N*-isopropylcarbamates.[89]

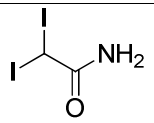
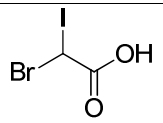
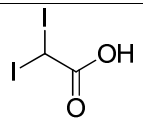
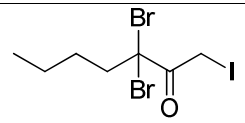
Antioxidant iodinated meroterpene **71** was isolated from Japanese red alga *Ascophyllum nodosum*.[90] From an ethyl acetate fraction of the brown alga *Cystophora retroflexa*, 2-iodophloroglucinol triacetate (**72**) was isolated.[86] An investigation of the red alga *Delisea pulchra* (Cape Banks, New South Wales, Australia), yielded iodinated furanones **73-75**.[91] The absolute configurations of **73-75** were determined by X-ray and CD spectroscopy.[92] Iodinated furanones **76** and **77** were isolated from red alga *D. fimbriata*.[93, 94] Non-volatile iodine was mainly concentrated from seawater in the peripheral tissues of brown algae. In Laminariales, several speciation studies have concluded that up to 90% of total iodine was mainly stored in a labile inorganic form identified as iodide, while the organic forms in *Laminaria* were dominated by hormone-like tyrosine derivatives, *i.e.*, monoiodotyrosine (MIT, **78**) and diiodotyrosine (DIT, **1**). The ubiquity of iodinated tyrosines (*e.g.*, MIT, DIT) across extant eukaryotic phyla has shown their general function as endocrine molecules involved in cell-cell communication (plants) as well as time-coordinated and dose dependent developmental changes.[95] Trophic transfers of thyroxine and thyroid hormone precursors from primary producers (possibly detected in phytoplankton upon immunological assays) to consumers were essential to the metamorphosis of larvae of marine invertebrates and gene regulation and signal transcription in vertebrates. Contrary to most organohalogenates of phaeophyte origin, tyrosine halogenations into

MIT **78** and DIT **1** was believed to occur spontaneously, they were not mediated by enzyme. They play an important role of signal mechanism in eukaryotic physiology,[95] make them possible candidates as hormone-like substances, along with known elicitors (alginate hydrolysates) of kelps.[61] MIT **78** and DIT **1** in marine algae were detected by coupling different chromatographic techniques with UV and ICP-MS.[96] One theory was that the simple marine haloalkanes, such as chloroform, bromoform, *etc*., arise from *in vivo* haloform reactions, which enable algae to secrete continuously these 'anti-predator' chemicals.[64]

239 Table 1. The names and structures of Compounds **2-78**.

240

No.	**2**	**3**	**4**	**5**
name	iodomethane	Diiodomethane	iodoform	dibromoiodomethane
Structure				
No.	**6**	**7**	**8**	**9**
name	bromodiidomethane	bromochloroidomethane	bromoiodomethane	carbonyl iodide
Structure				
No.	**10**	**11**	**12**	**13**
name	2-iodoethanol	1-bromo-2-iodoethane	iodoacetone	1-bromo-3-iodo-2-propanone
Structure				
No.	**14**	**15**	**16**	**17**
name	1,1-dibromo-3-iodo-2-propanone	1,3,3-tribromo-1-iodo-1-propene	1-iodo-4,4-dibromo-3-buten-2-one	bromoiodoacetamide
Structure				

No.	18	19	20	21
name	diiodoacetamide	bromoiodoacetic acid	diiodoacetic acid	3,3-dibromo-1-iodo-2-heptanone
Structure				
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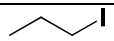
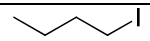
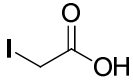
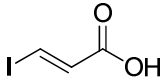
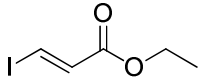
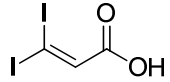
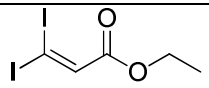
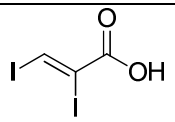
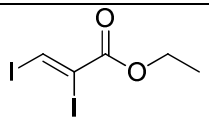
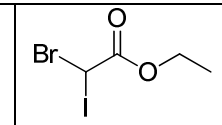
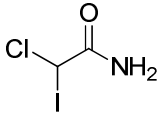
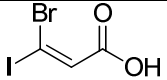
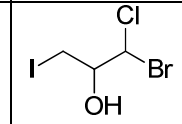
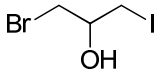
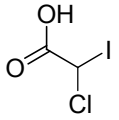
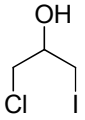
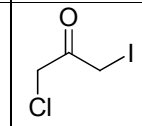
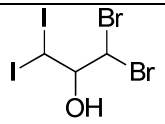
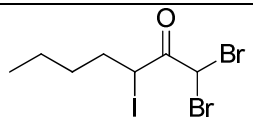
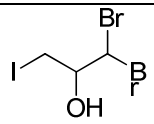
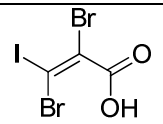
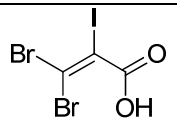
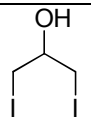
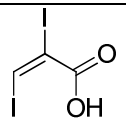
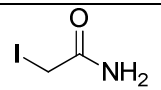
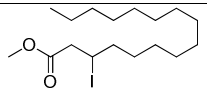
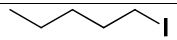
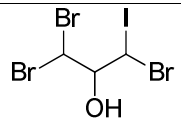
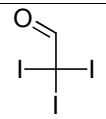
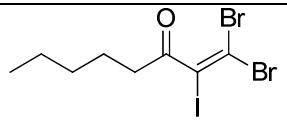
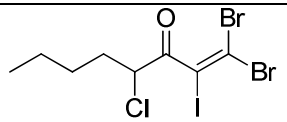
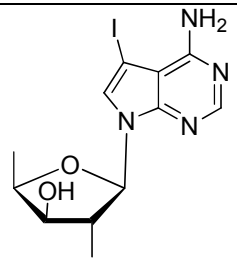
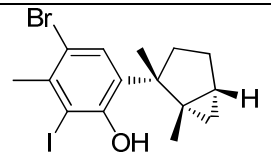
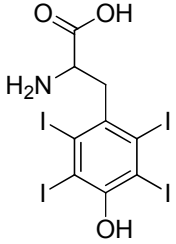
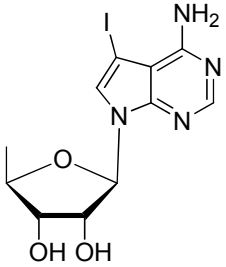
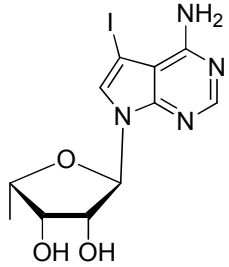
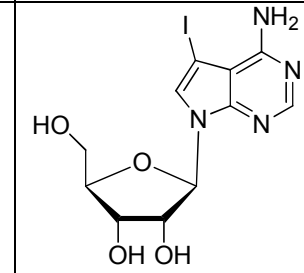
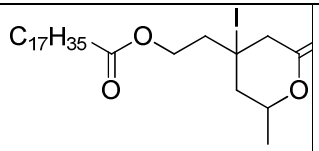
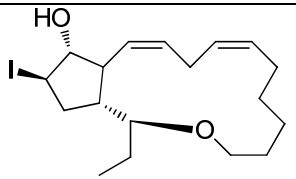
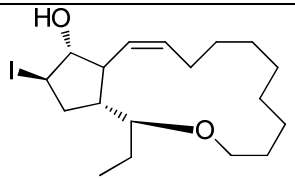
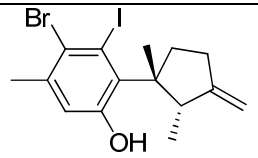
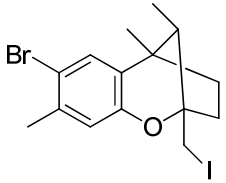
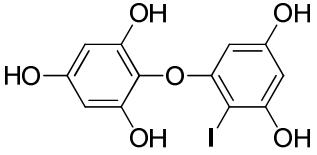
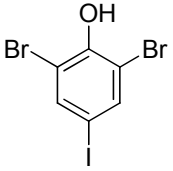
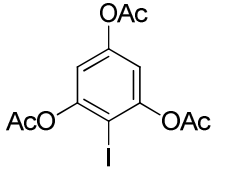
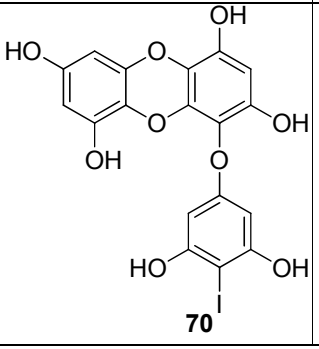
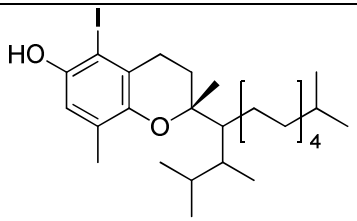
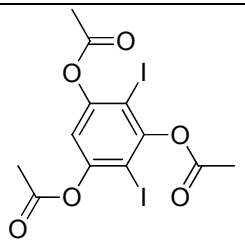
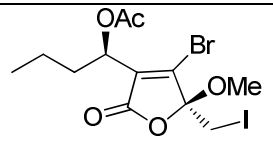
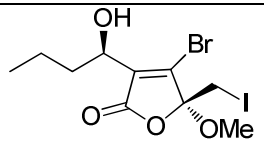
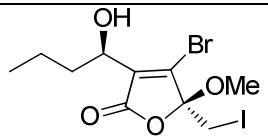
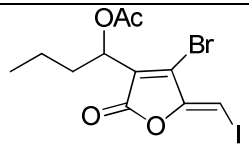
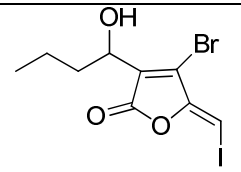
name	iodoethane	1-iodopropane	2-iodopropane	iodobutane
Structure				
No.	**26**	**27**	**28**	**29**
name	Iodoacetic acid	3-iodo-2-propenoic acid	ethyl ester of 3-iodo-2-propenoic acid	3,3-diiodoacrylic acid
Structure				
No.	**30**	**31**	**32**	**33**
name	ethyl ester of 3,3-diiodoacrylic acid	2,3-diiodo-2-propenoic acid	ethyl ester of 2,3-diiodo-2-propenoic acid	bromoiodoacetacetic acid ethyl ester

Structure				
No.	**34**	**35**	**36**	**37**
name	chloroiodoacetamide	2,3-dibromo-3-iodo-propenoic acid	chloroiodomethane	1-bromo-1-chloro-3-iodo-2-propanol
Structure				
No.	**38**	**39**	**40**	**41**
name	1-bromo-3-iodo-2-propanol	chloroiodoacetic acid	1-chloro-3-iodo-2-propanol	1-chloro-3-iodoacetone
Structure				
No.	**42**	**43**	**44**	**45**
name	1,1-dibromo-3,3-diiodo-2-propanol	1,1-dibromo-3-iodo-2-heptanone	1,1-dibromo-3-iodo-2-propanol	2,3-dibromo-3-iodo-2-propenoic acid

Structure				
No.	**46**	**47**	**48**	**49**
name	3,3-dibromo-2-iodo-2-propenoic acid	1,3-diiodo-2-propanol	2,3-diiodoacrylic acid	iodoacetamide
Structure				
No.	**50**	**51**	**52**	**53**
name	3-iodohexadecanoic acid methyl ester	1-iodopentane	1,1,3-tribromo-3-iodo-2-propanol	triiodoacetaldehyde
Structure				
No.	**54**	**55**	**56**	**57**
name	1,1-dibromo-2-iodo-1-octen-3-one	1,1-dibromo-4-chloro-2-iodo-1-octen-3-one	4-amino-7-(5'-deoxy-*β*-*D*-xylofuranosyl)-5-iodopyrrolo[2,3-d]pyrimidine	Aromatic sesquiterpene

Structure				
No.	**58**	**59**	**60**	**61**
name	2,3,5,6-tetroiodo-tyrosine	5'-deoxy-5-iodotubercidin	1′ α isomer of 5'-deoxy-5-iodotubercidin	5-Iodotubercidin
Structure				
No.	**62**	**63**	**64**	**65**
name	3-iodo-δ-lactone	Eiseniaiodide A	EiseniaiodideB	10-bromo-7-hydroxy-11-iodolaurene

Structure				
No.	**66**	**67**	**68**	**69**
name	iodoether A	2[D′]iododiphlorethol	dibromo-iodophenol	Iodophloroeckol
Structure				
No.	**70**	**71**	**72**	**73**
name	4′-iodoeckol	iodinated meroterpene	2-iodophloroglucinol triacetate	iodinated furanone
Structure	 **70**			

No.	**74**	**75**	**76**	**77**
name	iodinated furanone	iodinated furanones	Iodinated furanone	Iodinated furanone
Structure				
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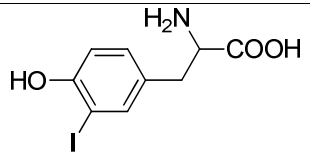
Structure				

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2.1.2. Sponges

The hydrophilic extract of the sponge *Ptilocaulis spiculifer* (Dakar, Senegal) has been shown to contain dakaramine **79**, a new tyrosine derivative containing iodine, an unusual feature for sponge metabolites.[97] Cyclodepsipeptide geodiamolide A (**80**)[98] was found in the Caribbean species of sponge *Geodia* (Rusts Bay, Trinidad and Tobago, West Indies), and showed antifungal activity against *Candida albicans*, with a minimal inhibitory concentration (MIC) at 31.3 μg/mL.[98] It has been efficiently synthesized from the polypropionate and tripeptide units using the Evans asymmetric alkylation, from the Mitsunobu esterification, and the macrolactamization with diphenyl phosphorazidate (DPPA) as key steps. Efficient esterification between the complex polyketide and tripeptide units was realized under high pressure conditions.[99, 100] Guided by cytoskeletal bioactivity, a reinvestigation of sponge *Auletta* sp. (Milne Bay, East Fields and Port Moresby Regions, Papua New Guinea) yielded geodiamolides A (**80**), D (**81**), and G (**82**), which were shown to cause microfilament disruption.[101] Geodiamolide D (**81**) was also isolated from Papua New Guinea sponge *Pseudaxinyssa* sp.[102] It was effective inhibitor of cellular proliferation in MDA-MB-435 cancer cells with IC_{50} value of 0.08 μg/mL.[101] The total synthesis of geodiamolide D (**81**)[103] was achieved. Geodiamolide G (**82**) was also identified from sponge *Cymbastela* sp. (Madang, Papua New Guinea), which showed activity against glioblastoma, astrocytoma U 373, and human ovarian carcinoma HEY.[104] Geodiamolide H (**83**) was isolated from the marine sponge *Geodia* sp (Macqueripe Bay, Trinidad). It dramatically affected the poorly differentiated and aggressive Hs578T cell line. It inhibits migration and invasion of Hs578T cells probably through modifications in actin cytoskeleton. Normal cell lines were not affected by treatment with **83**.[105] It showed *m vitro* cytotoxicities against a number of human cancer cell

lines: non small cell lung cancer, HOP 92 (118 nM); central nervous system, SF-268 (153 nM); ovarian cancer, OV Car-4 (18.6 nM); renal cancer, A498 (94.8 nM) and UO-31 (185 nM); and breast cancer MDA-MB-231/ATCC (433 nM) and HS 578T (245 nM).[106] Geodiamolides A (**80**) and H (**83**) were also isolated from *G. corticostylifera* (São Paulo State, Brazil). These peptides inhibited the first cleavage of sea urchin eggs (*Lytechinus variegatus*). Duplication of nuclei without complete egg cell division indicated the mechanism of action might be related to microfilament disruption. Further studies showed that geodiamolides A (**80**) and H (**83**) have anti-proliferative activity against human breast cancer cell lines, acted by disorganizing actin filaments of T47D and MCF7 cancer cells, keeping the normal microtubule organization. Normal cells lines (primary culture human fibroblasts and BRL3A rat liver epithelial cells) were not affected by the treatment compared to tumor cells, thus indicating the biomedical potential of the compounds.[107] Geodiamolides L (**84**), O (**85**), and R (**86**) have been isolated from the marine sponge *Cymbastela* sp (Motupore and Madang, Papua New Guinea). The serine residues of geodiamolides L (**84**), O (**85**), and R (**86**) have not been found previously in this family of compounds.[108] The cytotoxic peptide geodiamolide TA (**87**) was identified from the marine sponge *Hemiasterella minor* Kirkpatrick (Sodwana Bay, South Africa).[100] Neosiphoniamolide A (**88**) was isolated from the sponge *Neosiphonia superstes* (Banc Eponge Region, South of New Caledonia),[109] and proved to inhibit the growth of the fungi *Piricularia oryzae* and *Helmintbosporium gramineum* with IC_{90} value of 5 ppm.

Three cytotoxic depsipeptides, seragamides A, D, and E (**89-91**) have been isolated from the sponge *Suberites japonicus* (Seragaki and Manza, Okinawa Islands).

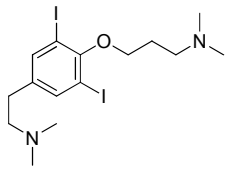
Seragamide A (**89**) promoted the polymerization of G-actin and stabilized F-actin filaments.[110]

The plakohypaphorines A–F (**92-97**) were isolated from the Caribbean sponge *Plakortis simplex* (Berry Island, Bahamas).[21, 111] Plakohypaphorine E (**96**) was the first naturally occurring triiodinated indole, while plakohypaphorine F (**97**) was a unique metabolite because it possessed both chlorine and iodine atoms on the indole nucleus. Plakohypaphorines A-F (**92-97**) were evaluated for antihistaminic activity on isolated guinea pig ileum. Plakohypaphorines B (**93**), C (**94**), and D (**95**) produced a significant concentration-dependent reduction of histamine-induced contractions. Under the same conditions, plakohypaphorine E (**96**) was much less active and its inhibitory effect showed no concentration dependence, while plakohypaphorines A (**92**) and F (**97**) were completely inactive. Although calculations of the values of pA_2 indicated a noncompetitive antagonistic effect, the histamine antagonism of **93-95** was specific because these molecules did not affect acetylcholine- and $BaCl_2$-induced contractions. The antihistaminic activity of **92-97** appeared to be connected to the number and nature of the halogen atoms on the aromatic nucleus. Indeed, only the diiodinated analogues proved to be consistently active, regardless the relative position of the halogen atoms. Interestingly, removal of one of the iodine atoms (in **92**), addition of a further iodine atom (in **96**), and substitution of an iodine atom with a chlorine atom (in **97**) caused a dramatic decay in the antihistaminic activity. The methanol extract of the Mediterranean tunicate *Aplidium conicum* (Sardinia, Italy) was also shown to contain plakohypaphorine A (**92**).[112] Topsentiasterol sulfate with iodinated side chain **98** was isolated from the marine sponge *Topsentia* sp. (Vang Fong Bay, Vietnam).[113] Plakohypaphorine E (**96**) was also isolated from the Caribbean sponge *Plakortis simplex* (The Coast of Bahama).[114] Iodinated metabolites

99 and **100**, derived from the tyrosine, have been isolated from Caribbean sponge *Iotrochota birotulata* (Little San Salvador Island, Bahamas).[115] *I. birotulata* was reported to contain significant amounts of iodine (0.12–1.21%),[115] together with comparable quantities of bromine (0.16–2.66%).[116] Hence, this supported the association of the iodometabolites with shows that high iodine amounts in the sponge tissue.[115]

Chemical investigation of marine sponges *Agelas linnaei* and *A. nakamurai* (Peniki E Island, Seribu Islands, Northwest Java, Indonesia) afforded the first iodinated tyramine-unit bearing pyrrole alkaloids, agelanesins B (**101**) and D (**102**). They exhibited cytotoxic activity against L5178Y mouse lymphoma cells with IC_{50} values at 9.25 and 13.06 μM, respectively.[117] It was challenging to find out why this *Agelas* sponge incorporated iodine into the agelanesins instead of bromine. This may be due to the iodide present in seawater, which was far below other halogens such as bromide and chloride. Despite its low concentration, unlike chloride, all known haloperoxidases were effective in oxidizing iodide.[118] Biosynthesis of iodinated metabolites seemed to be related to the capability of organisms to concentrate iodine from seawater, rather than to the presence of a specific peroxidase.[115] Two unprecedented phosphorus-containing iodinated polyacetylenes, phosphoiodyns A (**103**) and B (**104**), were isolated from a Korean marine sponge *Placospongia* sp. (near Tong-Yong city in the South Sea, Korea). Phosphoiodyn A exhibited potent agonistic activity on human peroxisome proliferator-activated receptor delta (hPPARδ) with an EC_{50} of 23.7 nM.[119, 120] The acetylenic acids with one (**105** and **106**) or two (**107** and **108**) iodine atom(s), were isolated from the marine sponges *Suberites mammilaris* and *S. japonicus* (Cheju Island, Korea). The methylated compounds **107** and **108** exhibited a strong NO inhibitory effect on RAW264.7 cells. While methylated **105**

and **106** were inactive in RAW264.7 cells, but highly active in BV2 microglia cells.[121] A new inhibitor, placotylene A (**109**), of the receptor activator of nuclear factor-B ligand (RANKL)-induced osteoclast differentiation, and a regioisomer of placotylene A, placotylene B (**110**), were isolated from a Korean marine sponge *Placospongia* sp. (near Tong-Yong city in the South Sea, Korea). Placotylene A (**109**) displayed inhibitory activity against RANKL-induced osteoclast differentiation at 10 μM while placotylene B (**110**) did not show any significant activity up to 100 μM, respectively.[122] 6′-Iodoaureol (**111**) was isolated from the Andaman Sea sponge *Smenospongia* sp. (PP Island, Krabi Province, Thailand), it is the first reported iodo–sesquiterpene hydroquinone.[123]



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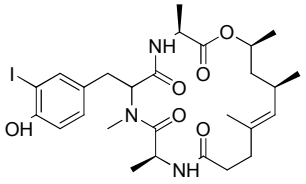

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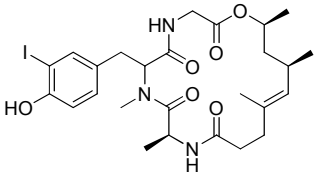

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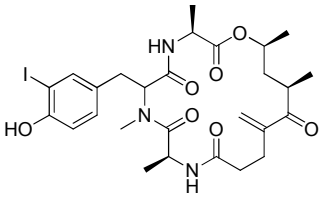

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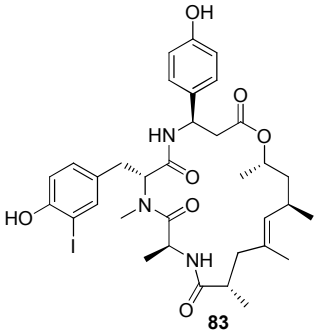

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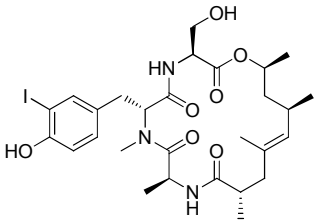

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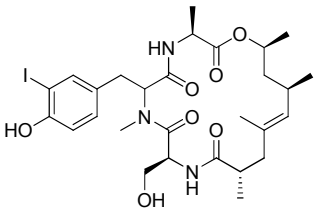

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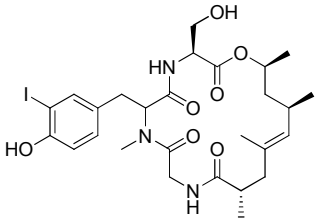

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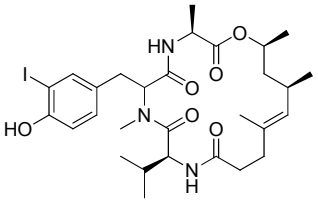

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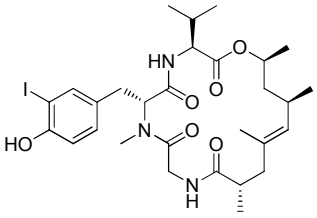

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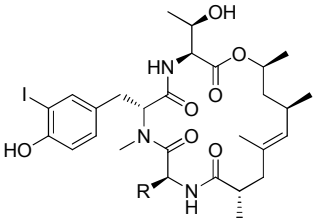
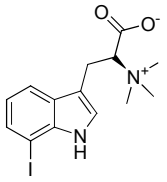


89 R = Me
90 R = H
91 R = CH_2OH



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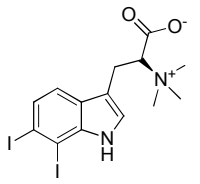

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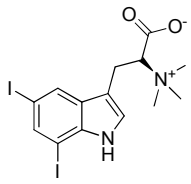

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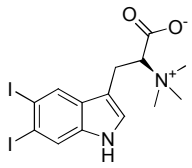

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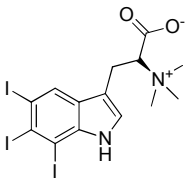

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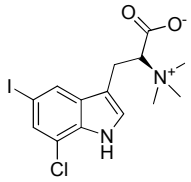

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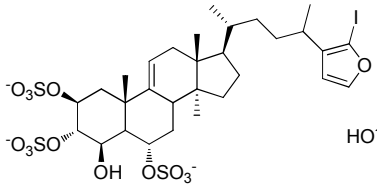

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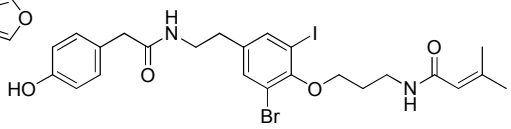

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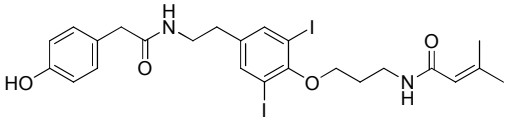

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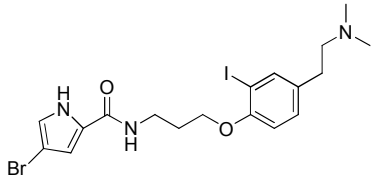

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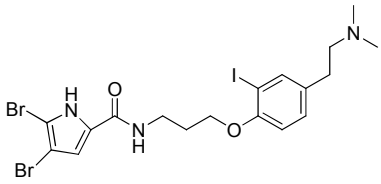

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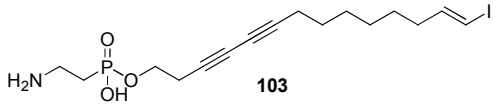

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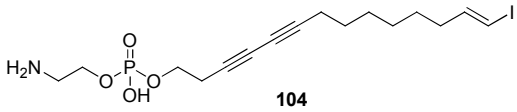

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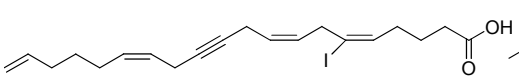

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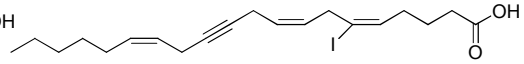

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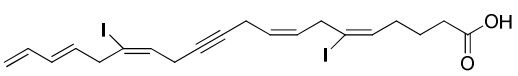

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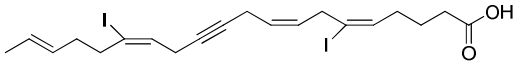

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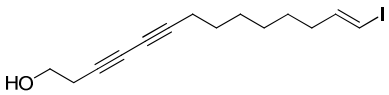

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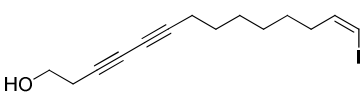

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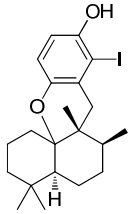

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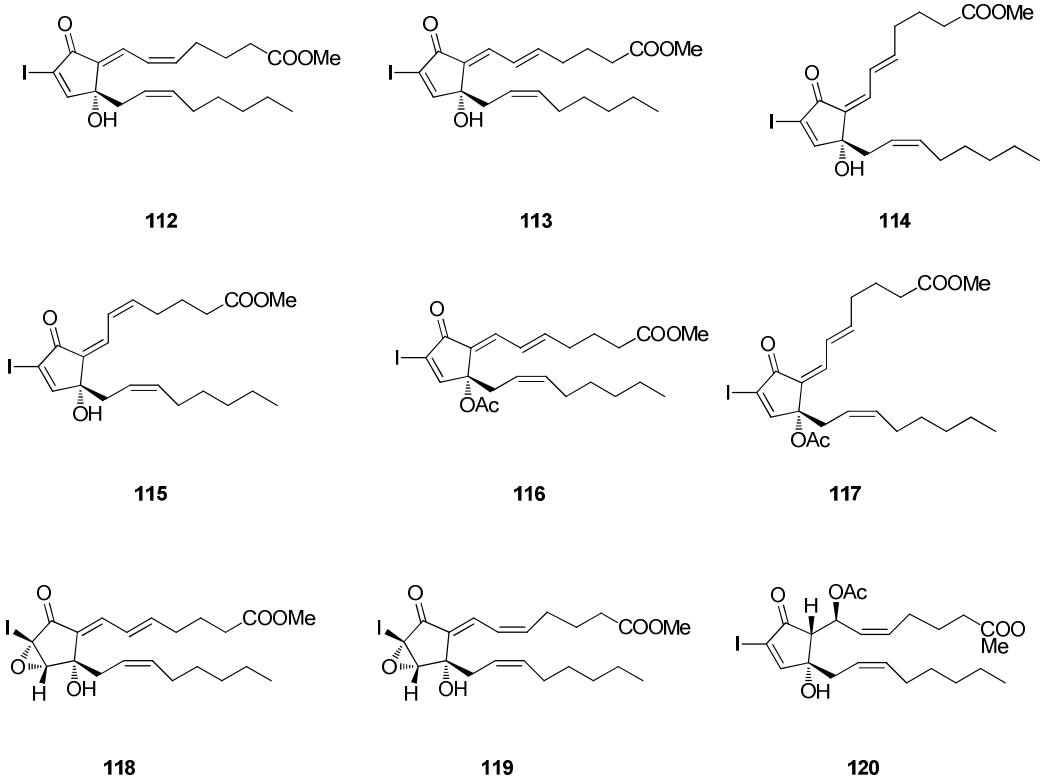
2.1.3. Cnidaria

The first reported halometabolite, 3,5-diiodotyrosine (**1**), was isolated from the coral *Gorgonia cavolii* in the late nineteenth century.[13, 124, 125] Iodovulone-I (**112**), a unprecedented iodinated marine prostanoid with antitumor activity was isolated from the soft coral *Clavularia viridis* Quoy and Gaimard (Okinawa Islands).[126, 127] Iodinated prostanoids iodovulone II, iodovulone III, iodovulone IV, 12-*O*-acetyliodovulone II, 12-*O*-acetyliodovulone III, 10,11-epoxyiodovulone II, and 10,11-epoxyiodovulone I (**113-119**) were isolated as minor constituents from *C. viridis* (Ishigaki, Okinawa Islands).[128] Iodovulone II (**113**) showed cytotoxic activity against human T lymphocyte leukemia (MOLT-4), human colorectal adenocarcinoma (DLD-1), and human diploid lung fibroblast (IMR-90) cells at IC_{50} values 0.52, 0.6, and 4.5 μg/mL, respectively. Bioassay-directed fractionation of the CH_2Cl_2-MeOH extract of *C. viridis* (Green Island, Taiwan) has also afforded iodovulones II (**113**) and III (**114**). Iodovulone II (**113**) exhibited the cytotoxicity against human prostate (PC-3) and colon (HT29) cancer cells with IC_{50} values 3.9 and 6.5 μM. Iodovulone III (**114**) exhibited the cytotoxicity against PC-3 and HT29 cancer cells with IC_{50} values 6.7 and 10.0 μM, respectively.[129] Iodinated prostanoids 7-acetoxy-7,8-dihydroiodovulone I (**120**) and 7-acetoxy-7,8-dihydroiodovulone II (**121**) were isolated from *C. viridis* (Ishigaki, Okinawa Islands). Compound **120** demonstrated cytotoxic activity against MOLT-4, DLD-1, and IMR-90 cells at IC_{50} values 0.5, 0.6, and 4.5 μg/mL, respectively.[130] The first iodine-containing briaranes to be found in nature were dichotellides A-E (**122-126**) from South China Sea gorgonian *Dichotella gemmacea* (Meishan Island, Hainan Province, China). Dichotellide C (**124**) showed marginal activity against human pancreatic (SW1990) cancer cells (IC_{50}, 45.0 μM).[131] Four naturally produced organoiodides, fragilisinins I-L (**127-130**) were isolated from the

South China Sea gorgonian *Junceella fragilis* (Meishan Island, Hainan province of China). Fragilisinin J **128** had potent antifouling activities at nontoxic concentrations with EC_{50} values of 11.9 μM.[132]

Novel eight-membered heterocycles, named hicksoanes A-C (**131-133**),[133] were isolated from the Red Sea gorgonian *Subergorgia hicksoni* (Gulf of Aqaba, Eilat, Israel). Hicksoanes A-C (**131-133**) showed antifeeding activity against goldfish at natural concentration 10.0 μg/mL. The biosynthesis of hicksoanes A-C (**131-133**) proceeded presumably under the participation of haloperoxidases and nonribosomal peptide biosynthetic machinery. Both haloperoxidases producing hypohalogenic acid as the actual halogenating agent and NADH dependent halogenases transforming the substrate so that the halide ion may be used directly as a nucleophile has been proposed to catalyze the reaction.[134] An unusual structure containing a combination of indole–oxazole–pyrrole unit, breitfussin A (**134**) was isolated from the hydrozoan *Thuiria breitfussi* (Bjørnøya, Bear Island, Norway).[135]



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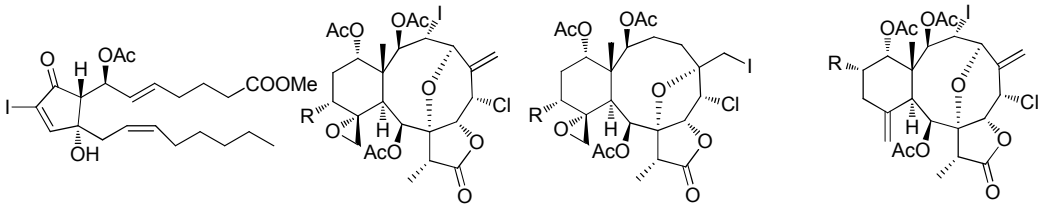

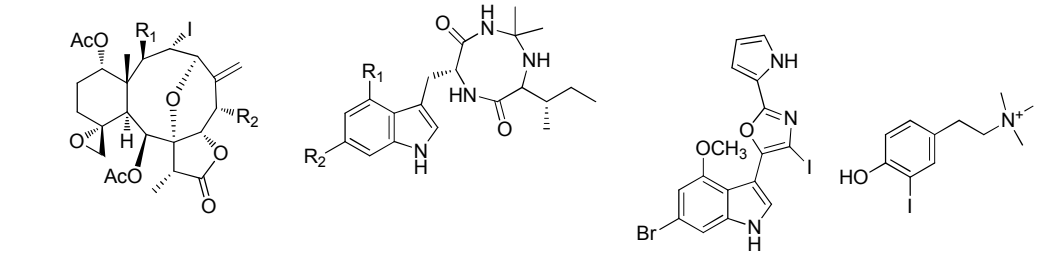

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396 **2.1.4. Tunicates (ascidians)**

397 Chemical investigation of the Mediterranean ascidian *Ciona edwardsii* (Bay of

398 Naples, Meta di Sorrento, Punta Gradelle, Italy) has been performed, leading to the

isolation of tyrosine derivative iodocionin (**135**), which was shown to possess significant and selective activity against lymphoma cells with an IC_{50} of 7.7 μg/mL.[136] Non cytotoxic triphenylpyrrolo-oxazinone, lukianol B (**136**), was isolated from a tunicate (the lagoon of Palmyra Atoll).[137] Recently, Fuente and co-workers screened about two thousand marine natural products to find out structurally novel human aldose reductase (h-ALR2) inhibitors.[138] They reported lukianol B (**136**) was the most potent one among the compounds tested. Its h-ALR2 inhibitory activity (IC_{50}=0.6 μM) was six-fold more potent than that of the known ALR inhibitor sorbinil. The therapeutic effects of h-ALR2 inhibitors for some degenerative complications of diabetes, such as neuropathy, nephropathy, and retinopathy, are well recognized. Therefore, lukianol B (**136**) can be regarded as a new lead to develop therapeutic agents for treatment of these disorders. Total synthesis of lukianol B (**136**) has been achieved using *N*-benzenesulfonyl-3,4-dibromopyrrole as a common starting material. The key synthetic strategy developed is the combined bromine-directed lithiation and palladium-catalyzed cross-coupling of *N*-benzenesulfonyl-3,4-dibromopyrrole to produce 3,4-diarylpyrrol-2-carboxylates.[139] A nucleoside **56** was isolated from an ascidian *Diplosoma* sp. (Hateruma, Okinawa Islands) and its structure was successfully determined by spectroscopic and chemical analysis, **56** was found to inhibit the division of fertilized sea urchin eggs.[140] **56** and **59** were also isolated from two unrelated marine organisms, the ascidian *Diplosoma* sp and the alga *Hypnea valendiae*.[72] **58** was an iodinated tyramine derivative which constituted one of the main components isolated in several samples of tunicates of the genus *Didemnum* (Barrang Lompo, Indonesia).[73, 74] Iodinated phenethylamine (**137**) and the corresponding phenethylamine urea **138** were isolated from a tunicate *Didemnum* sp (Northwest end of Cocos Lagoon, Guam), **137** showed *in vitro* activity against the

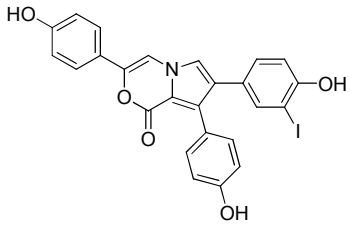
yeast *Candida albicans* and was mildly cytotoxic against tumor cell line L1210 with IC_{50} 20 μg/mL.[141] 5′-Deoxy-3-iodotubercidin (**59**) and **60** were identified from the ascidian *Didemnum voeltzkowi* (Apo Reef, Philippines).[142] An Australian species of ascidian *Aplidium* sp. has yielded three iodinated *L*-tyrosine derivatives **139-141**.[143] The study of an aqueous extract from the ascidian *Didemnum rubeum* (Reef & Islands of Chuuk Atoll, Micronesia) permitted the isolation of previously reported diiodo-tyramine derivative **137** and **138** together with iodo-tyramine derivatives **142-148**.[144] Polyandrocarpamide B (**149**) was isolated from the marine ascidian *Polyandrocarpa* sp. (Siquijor Islands, Philippines).[145] Plakohypaphorine A (**92**) was isolated from the methanol extract of the Mediterranean tunicate *Aplidium conicum* (The coast of Sadinia, Italy).[146]

2.1.5. Mollusk

Bioassay-guided separation of the aqueous ethanol extract of the viscera of the gastropod *Turbo marmorata* (Okinawa Islands) resulted in the isolation of two toxins, turbotoxins A (**150**) and B (**151**), isolated as bis-trifluoroacetates.[147, 148] The structures were determined by spectral analysis and confirmed by organic synthesis to be diiodotyramine derivatives. Turbotoxins A (**150**) and B (**151**) exhibited acute toxicity against ddY mice, with LD_{99} values of 1.0 and 4.0 mg/kg, respectively.[147] The structure-toxicity relationship of turbotoxins was examined, and it was proved that the iodine atoms and trimethylammonium groups were important for its acute toxicity. Turbotoxin A (**150**) inhibited acetylcholinesterase with an IC_{50} of 28 μM.[148] X-Ray crystallographic studies of complexes of acetylcholinesterase with small molecules,

such as decamethonium bromide, tacrine, and edrophonium bromide, indicated that the aromatic gorge exists at the bottom of the active site. There was as yet no data of relationships between the toxicity and affinity to acetylcholinesterase of turbotoxin analogs, however, the benzyl group might be stacked against the aromatic gorge to increase its toxicity. Preliminary neuropharmacological experiments were effected for turbotoxin A (**150**), it was proved not to interact with the peripheral nervous system. The toxin iodomethyltrimethylammonium chloride (**152**) was found in the viscera of the green turban shell *Turbo marmorata* (Ishigaki, Okinawa Islands).[149] A cytotoxic cyclodepsipeptide, doliculide (**153**), was isolated from the sea hare *Dolabella auricularia* (Mie Prefecture, Japan).[150] It contained a 15-carbon polyketide unit, glycine, and a unique *D*-amino acid, regarded as a metabolite of mixed peptide-polyketide biogenesis. It was noteworthy that doliculide (**153**) possessed a structurally novel polyketide moiety and exhibited potent cytotoxicity against HeLa-S_3 cells with an IC_{50} of 0.001 μg/mL.[150] The first total synthesis of doliculide (**153**) has been achieved.[151] The key step of the synthesis was the construction of the stereogenic centers of a 15-carbon polyketide-derived dihydroxy acid moiety by a combination of the Evans aldol reaction and the Barton deoxygenation reaction. Furthermore, artificial congeners of doliculide (**153**) were synthesized and the structure-cytotoxicity relationships were examined.[152]

Iodinated furanones **76** and **77** were isolated from the sea hare *Aplysia parvula* and its host plant *Delisea pulchra* (Sydney, New South Wales, Australia).[153] The results indicated that the distribution and level of *D. pulchra* metabolites in *A. parvula* were consistent with a role as acquired chemical defenses against predators.



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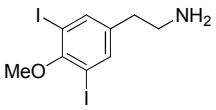

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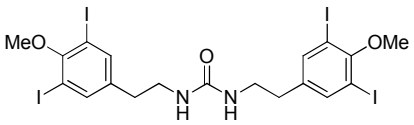

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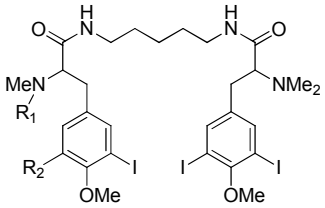
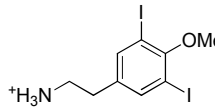


139 R_1 = Me, R_2 = H
140 R_1 = Me, R_2 = I
141 R_1 = R_2 = H



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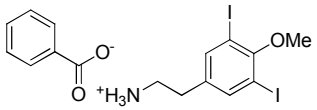

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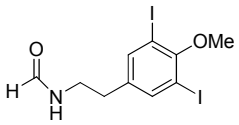

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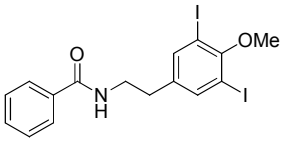

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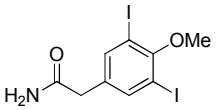

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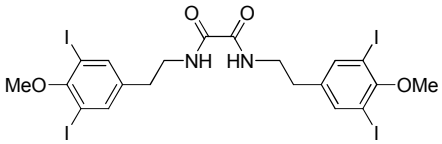

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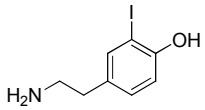

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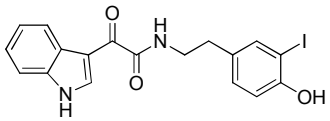

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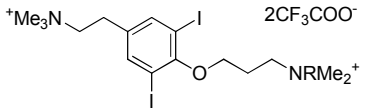

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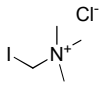
151 R = H



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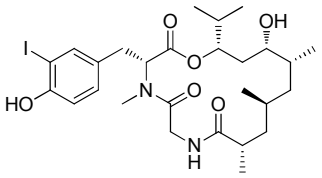


153

2.1.6. Bacteria

The iodoalkaloid 3,6-diiodocarbazole (**154**) was isolated from the marine cyanobacterium *Kyrtuthrix maculans* (Ping Chau, Hong Kong, China).[154] Synthesis of the iodocarbazole was achieved by direct iodination of carbazoles by *N*-iodosuccinimide and *N*-iodosuccinimide-silica gel system.[155] Tasihalides A (**155**)

and B (**156**), possessing a novel cage structures, have been isolated from an assemblage of a marine cyanobacterium belonging to the genus *Symploca* and an unidentified red alga (Short Drop-off, Palau).[20] The presence of iodine was confirmed by the UV/vis spectrum, which showed an *n*-σ* transition at 253 nm characteristic of this halide. The closest structural relatives to tasihalides A (**155**) and B (**156**) were tricyclic synthetic compounds that have been prepared from cembrane diterpenes treated with electrophiles.[156] This made it tempting to speculate that tasihalides A (**155**) and B (**156**) arose from a halogenation-initiated cyclization of an oxygenated cembrane diterpene. Such haloperoxidase-mediated electrophilic cyclizations have recently been demonstrated *in vitro* using bromoperoxidases cloned from red algae.[157]

A slightly halophilic myxobacterial strain, *Paraliomyxa miuraensis* SMH-27-4 (Brush Vegetation, Arai-Hama Beach, Miura Peninsula, Kanagawa Prefecture, Japan), was isolated. This slowly growing myxobacterium produced the antibiotic depsipeptide miuraenamide B (**157**), which inhibited NADH oxidase with IC_{50} value of 50 μM.[158, 159] Miuraenamide B (**157**) inhibited selectively the fungus-like phytopathogen *Phytophthora capsici* at a minimum dose of 0.025 μg per disk and had no effect on bacteria. Several polyketide-peptide hybrid-type metabolites that resemble the miuraenamides have been isolated from marine sponges and a mollusk (*e.g.*, geodiamolides, seragamides, and doliculide). The true producers of these metabolites could be unknown halophilic myxobacteria and/or related microorganisms.[158, 159]

2.2. Terrestrial organisms

2.2.1. Actinomyces

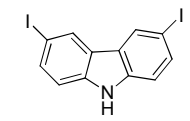
The calicheamicins (CLMs) α_2^I (**158**), α_3^I (**159**), β_1^I (**160**), γ_1^I (**161**), and δ_1^I (**162**),[160-163] were a class of enediyne antibiotics derived from the terrestrial bacterium

Micromonospora echinospora (Chalky soil, Kerrville, Texas, USA), with CLM γ_1^I (**161**) being the most notable. It was extremely toxic to all cells, a CD33 antigen-targeted immunoconjugate *N*-acetyl dimethyl hydrazide CLM was developed and marketed as targeted therapy against the non-solid tumor cancer acute myeloid leukemia (AML).[164] CLM γ_1^I (**161**) was one of the most potent known antitumor agents. Its extremely potent cytotoxic properties led to its development as an antibody drug conjugate (ADC, Mylotarg®) against a certain type of leukemia. Introduced in 1996, Mylotarg ® was the first drug in the clinic ushering in a new era of cancer chemotherapy that now constituted one of the most active areas of cancer research and already boasted of several promising drug candidates in the pipeline.[165-167]

Total synthesis of CLM γ_1^I (**161**) was achieved.[168] An account of the reasoning and reduction to practice of a highly convergent total stereospecific synthesis of CLM γ_1^I (**161**) was provided. The key finding was the use of a very mild promoter system to allow for coupling of trichloroacetimidate with advanced calicheamicinone-like accepters.[169]

The enediyne antibiotic CLM γ_1^I (**161**) was targeted to DNA by a novel aryltetrasaccharide comprised of an aromatic unit and four unusual carbohydrates. CLMs binded with DNA in the minor groove, where they then underwent a reaction analogous to the Bergman cyclization, generating a diradical species. Like all enediynes, this diradical, 1,4-didehydrobenzene, then abstracted hydrogen atoms from the deoxyribose (sugar) backbone of DNA, which resulted in strand scission.[170] The core metabolic pathway for biosynthesis of this molecule resembled that of other characterized enediyne compounds and occurred *via* a polyketide synthase pathway.[171] The specificity of binding of CLM to the minor groove of DNA was demonstrated to be due to the aryltetrasaccharide group of the molecule.[172, 173]

The headspace extracts from *Streptomyces chartreusis* (Braunschweig, Germany) contained methyl 2-iodobenzoate (**163**), an iodinated volatile.



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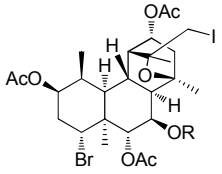

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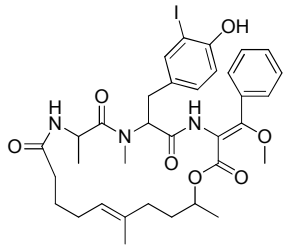
156 R = Ac



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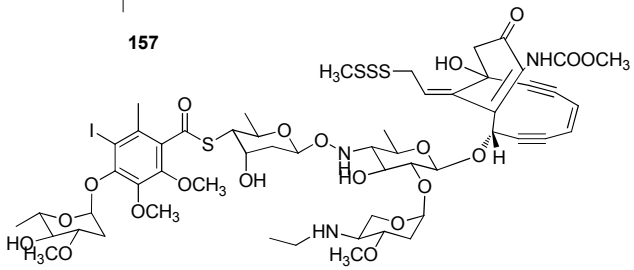

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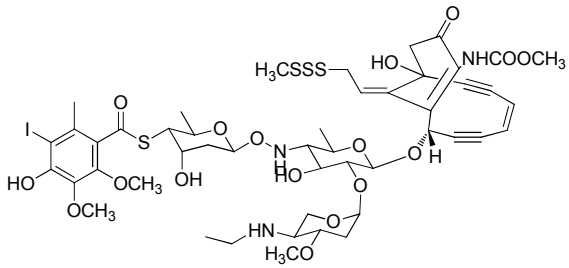

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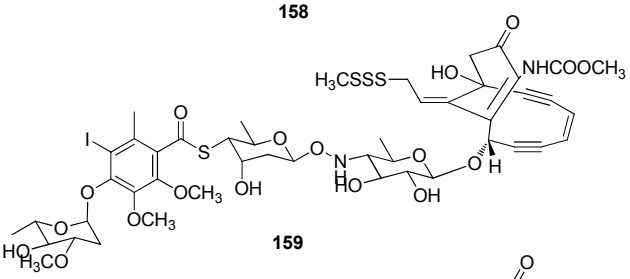

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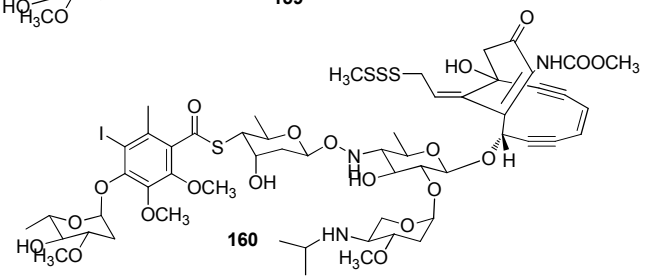

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2.2.2. Insects

Several insects contained monoiodohistidine (MIH), 2-iodohistidine (**164**) and 4-iodohistidine (**165**) obtained from the cuticle of locusts.[2] 2-(or 4)-Iodohistidine (**164**)

535 or (**165**) have been found in several insects such as the squash bug, house fly,
536 mosquito, dragonfly, and cockroach.[174, 175]

537 **2.2.3. Higher animals**

538 Organoiodines are rare in higher animals. However, several such compounds have
539 been identified. 3-Mono-iodo-4-hydroxyphenylpyruvic acid (**166**) and
540 3,5-di-iodo-4-hydroxyphenylpyruvic acid (DIHPPA, **167**) were isolated from rat
541 thyroid glands.[176, 177] 4-Iodohistidine, phosphoriodohistidine (PIH, **168**), thyroxine
542 [O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-*L*-tyrosine, T4, **169**], and
543 3,5,3′-triiodothyronine (T3, **170**) were extracted from beef heart mitochondria.[178, 179]
544 4-Iodohistidine (**165**) was the product of limited iodination of histidine,[180] PIH (**164**)
545 was a possible intermediate of oxidative phosphorylation by rapid ^{32}P-labeling
546 experiment.[181] Thyroxine (**169**) and 3,5,3′-triiodothyronine (**170**) have been also
547 shown to be present in butanol extracts of normal rat liver, kidney, and heart.[182] MIH
548 (**164** or **165**) and diiodohistidine (DIH, **171**) were identified from thyroidal
549 iodoproteins and their peripheral metabolism in rats.[183] Behavior of deiodination of
550 DIH (**171**) in the presence of liver and kidney homogenates of the rat was studied
551 qualitatively in terms of time course on thin layer chromatography and paper
552 chromatography comparing with the known course of metabolism of DIT (**1**).
553 Differing from DIT (**1**), iodine was split from DIH (**171**) depending neither on the
554 amount of homogenate or time course. In order to examine the mode of deiodination
555 from DIH (**171**) and MIH (**164** or **165**) more precisely, they were labeled with ^{131}I,
556 and the metabolism of DIH (**171**) and MIH (**164** or **165**) was found to be considerably
557 different. DIH (**171**) was deiodinated enzymically and non-enzymically, but MIT (**78**)
558 resisted rapid metabolism, and it was deiodinated slowly in the body.[184, 185] The
559 2-iodohexadecanal (2-IHDA, **172**) was present in the horse, dog, and rat thyroids.[186]

Studies indicated that **172** served as a mediator of some of the regulatory actions of iodide on the thyroid gland.[187, 188] Pereira *et al*.[186] 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-IHDA (**172**). The biosynthesis of the iodolipid was likely to involve the addition of iodine to the vinyl ether group of plasmenylethanolamine. It mimicked the main regulatory effects of iodide on thyroid metabolism: inhibition of H_2O_2 production of adenylyl cyclase. 2-Iodohexadecan-1-ol (2-IHDO, **173**) was also detected in these studies, it was formed later than 2-IHDA (**172**), and thyroid cells converted exogenous 2-IHDA (**172**) into 2-IHDO (**173**) in a time-dependent way, the ratio of 2-IHDO/2-IHDA increased with H_2O_2 production and decreased as a function of iodide concentration. An aldehyde-reducing activity was detected in subcellular fractions of the horse thyroid. No formation of 2-iodohexadecanoic acid could be detected, reduction into the biologically inactive 2-IHDO (**173**) was thus a major metabolic pathway of 2-IHDA (**172**) in dog thyrocytes.[189]

(2*R*)-(+)- and (2*S*)-(-)-2-IHDA (**172**) were synthesized[190] in five steps and 62% overall yield from chiral enol ethers, *via* the iodocyclization and chromatographic separation of the resulting diastereomeric 1'-iododioxanes. The absolute configuration has been assigned through chemical correlation and by application of Mosher's method to the esters obtained by methanolysis of (2*R*)- and (2*S*)-2-IHDA, respectively, followed by derivatization. Moreover, the biosynthesis and the inhibitory activity have been shown to be unstereoselective.[191]

Another α-iodoaldehyde, 2-iodooctadecanal (**174**), was also detected in the rat and dog thyroids where it was even more abundant than 2-IHDA (**172**).[186]

6-Iodo-5-hydroxy-eicosatrienoic acid, δ-lactone (**175**) and

5-iodo-4-hydroxydocosapentaenoic acid, γ-lactone (**176**) have been identified in the thyroid gland of dogs.[192] The transformation of arachidonic acid and docosahexaenoic acid with lactoperoxidase, iodide, and hydrogen peroxide into **175** and **176** *in vitro* suggested that this pathway may operate *in vivo* with thyroid peroxidase.[3]

Although existence of the thyroid gland has been known for hundreds of years, the first report linking cretinism and hypothyroidism to the destruction of this gland was published in 1888.[193] The existence of hormone containing iodine as a normal constituent of the thyroid gland was foretold by Baumann in 1895,[194] the first report of the isolation of thyroxine (**169**) from mammalian thyroid gland was published in 1915,[195] followed by later publications identifying a few related iodinated tyrosines (**170**) and 3,5-diiodothyronine (**177**).[196, 197] But it was Kendall[195, 198, 199] in 1919, who first isolated the hormone *via* alkaline hydrolysis of hog thyroid glands and named the compound, 'Thyroxine'. Kendall successfully isolated 7 g of crystalline thyroxine (**169**). Later, Harington and co-workers[196, 200, 201] employed an enzymatic hydrolysis to liberate the thyroxine (**169**) from hog thyroid glands, and correctly reported its empirical formula to be $C_{15}H_{11}O_4NI_4$. They also reported the correct structure of the isolated thyroxine (**169**) based on extensive analysis and subsequently an independent chemical synthesis. Similar structural elucidation results on thyroxine (**169**) were also obtained by Foster *et al.*,[202] who employed an acid hydrolysis following a brief enzymatic digestion of the hog thyroid gland. The stereochemistry of this α-amino acid was designated to be *L*-series by Canzanelli *et al.*,[203] who found similar optical rotations for two *L*-thyronine, which were prepared by conversion of natural thyroxine (**169**) isolated from thyroid gland, and synthesized from *L*-tyrosine.

Iodolipids in calf thyroid slices were characterized as iodinated free fatty acids and neutral lipids.[204] Suppression of iodine organification as well as phospholipase A_2

strongly decreased their formation, whereas inhibition of prostaglandin synthesis increased lipid iodination, suggesting a correlation to the arachidonic acid metabolism.[205] Transformation of arachidonic and docosahexaenoic acids by the action of lactoperoxidase, iodine and hydrogen peroxide into iodolactones have been demonstrated *in vivo*.[205, 206] Lactoperoxidase catalyzed 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 were: *δ*-lactone of 6-iodo-5-hydroxy-eicosatrienoic acid (**175**) and *γ*-lactone of 5-iodo-4-hydroxydocosapentaenoic acid (**176**).[204] Also two other *ω*-lactones (**178**) and **179** have been detected by GC–MS.[192, 204] Pereira *et al.*[186] have been demonstrated the formation of iodolipids (*ω*-lactone of 14-iodo-15-hydroxy-eicosa-5,8,11-trienoic acid (**178**) and *ω*-lactone of 15-iodo-14-hydroxy-eicosa-5,8,11-trienoic acid (**179**) by incorporation of iodine into proteins and lipids of horse thyroid slices. The authors have identified the major thyroid iodolipid to be 2-IHDA (**172**). The biosynthesis of the iodolipid was likely to involve the addition of iodine to the vinyl ether group of plasmenylethanolamine. *δ*-Iodolactones decreased epidermal growth factor-induced proliferation and inositol-1,4,5-trisphosphate generation in porcine thyroid-follicles.[207]

Thyroxine (**169**), and other iodinated tyrosine (**170**), and 3,5-diiodothyronine (**177**) have been isolated from numerous ascidians, sponges, gorgonians, marine algae, and insects.[2, 11, 208, 209]

2.2.4. Human

Iodine was considered as essential mineral in the human body. MIH (**164** or **165**) and DIH (**171**) were identified from thyroidal iodoproteins and their peripheral metabolism in normal man.[183] MIH (**164** or **165**) and DIH (**171**) were identified from

the urine of patients with congenital goitrous hypothyroidism.[210] 3,5-Diiodotyrosine (**1**) has been shown to be the second stage of iodine incorporation into the amino acid tyrosine in the thyroid glands. The action of the enzyme thyroid peroxidase on tyrosine in the presence of iodine first produced 3-iodotyrosine, which is the precursor to 3,5-diiodotyrosine (**1**). Two 3,5-diiodotyrosine molecules then combined in the presence of this same enzyme to generate 3,5,3′,5′-tetraiodothyronine, commonly known as thyroxine (**169**).[125]

Thyroxine (T4, **169**) was an essential hormone produced by the thyroid gland, which presented in humans, was located in the neck just below the larynx. The thyroid gland utilizes iodine, primarily from food (*e.g.*, seafood, bread, and salt) to produce T4 along with small amounts of 3,5,3′-triiodothyronine (T3, **170**), in about 99.9:0.1 ratio, respectively. T3 exhibited most of the physiological activity and it was primarily produced by deiodination of T4 in tissues other than the thyroid gland. T3 has a much shorter half-life, less than two days, when compared to T4. The thyroid hormones, T4 and T3, were the only two endogenous hormones containing iodine atoms. Thyroid hormones regulated a variety of metabolic processes and played a critical role in normal growth and development, carbohydrate metabolism, oxygen consumption, and maturation of the central nervous system and bone. Indeed, these hormones were required for normal function of nearly all tissues.[193]

Biosynthesis of thyroxine (**169**) has been the subject of continued investigation for decades, and the precise mechanism of this interesting biochemical process is not yet fully understood. The coupling of two 3,5-diodotyrosine (DIT, **1**) molecules to form thyroxine (**169**) was first suggested as early as 1927 by Harington and Barger.[200] Subsequently, von Mutzenbecher[211] in 1939 reported that the incubation of a basic solution of DIT (**1**) produced a small amount of thyroxine (**169**). Two possible

mechanisms, intra- and intermolecular coupling processes, were subsequently proposed for the *in vivo* formation of thyroxine (**169**) in the thyroid gland, which was catalyzed by the enzyme thyroid peroxidase (TPO).[212-215] Later studies indicated that peptide linked DIT (**1**) within thyroglobulin (TGB) was more likely the precursor of thyroxine (**169**).[216, 217] It was generally believed that thyroxine (**169**) was formed *via* oxidative free radical coupling[214, 215] of the phenol groups from two units of DIT (**1**) with the loss of a three-carbon unit, which was later reported by Johnson and Tewkesbury,[214] to be pyruvic acid. Subsequently, other groups reported identification of the three-carbon unit, which was lost in the transformation of DIT (**1**) into thyroxine (**169**) as alanine,[218] serine,[219] hydroxypyruvic acid,[220] and dehydroalanine.[221, 222] For some time, dehydroalanine was favored as the lost three-carbon unit in the biosynthesis of thyroxine (**169**). However, Sih and co-workers[223] recently showed that the three-carbon unit lost in this coupling process was in fact aminomelonic acid semialdehyde and further suggested that both intra- and inter-molecular mechanisms could be operating in the biosynthesis of thyroid hormones.

The first synthesis of (±)-thyroxine (**169**), was achieved by Harington and Barger[200] in 1927 in eight steps starting from 4-methoxyphenol. The synthesis began from 4-methoxyphenol, which was coupled with 3,4,5-triiodonitrobenzene and subsequently reduced the nitro group to give the corresponding aniline derivative. The amine group was then converted to a nitrile *via* diazotization, which upon reduction with anhydrous stannous chloride gave 3,5-diiodo-4-(4′-methoxyphenoxy) benzaldehyde. The arylaldehyde derivative was further reacted with hippuric acid in the presence of fused sodium acetate and further treated with sulfuric acid in ethanol to afford a cinnamic ester derivative. The olefin in ester was reduced using red

phosphorous in hydrochloric acid, which also hydrolyzed the benzamide and ethyl ester groups. The resulting product was treated with iodine and potassium iodide in aqueous ammonium hydroxide solution to afford (±)-thyroxine (**169**). This synthesis gave racemic hormone for comparison with the material isolated from thyroid gland and ultimately paved the way for confirmation of the structure of thyroxine (**169**). Harington[224] also prepared *L*-thyroxine *via* optical resolution starting from (±)-3,5-diiodothyronine (**177**), which was synthesized, was converted to the corresponding *N*-formyl derivative by treating with formic acid and then resolved using *L*-1-phenylethylamine to give the corresponding 3,5-diiodo-*L*-thyronine derivative. Hydrolysis of 3,5-diiodo-*L*-thyronine derivative and subsequent iodination afforded the *L*-thyroxine in its natural form thus again confirming the stereochemistry of the lone chiral center.

The persistent interest for thyroid iodolipids was related to speculations about their role in thyroid metabolism and regulation. It was suggested that they could play a role in the transport of iodide or be intermediates in thyroxine (**169**) formation. Alternatively, their formation might result from the nonspecific binding of oxidized forms of iodine and could thus play a protective role in scavenging excess iodine released by the thyroid peroxidase.[186, 206] It was also suggested that iodolipids could be the mediators of the Wolff-Chaikoff effect and other inhibitory effects of iodide on the thyroid gland, such as inhibition of iodide transport, adenylate cyclase activation, and hormone secretion.[186, 225]

2.2.5. Miscellaneous

Metaquat (1,1′-dimethyl-3,3′-bipyridinium diiodide, **180**) was isolated from an arrow poison (The poison is produced by squeezing chilli leaves, bark and a root crop) used by the Southeast Asian Orang Mentawai Tribe (The inhabitants of Siberut, an

island in the Mentawaiarchipelago, west of Sumatra), whose description of the effect of their poison was similar to that of curare, have the strong muscle relaxing effect. Metaquat (**180**) was isomeric with the common herbicide paraquat (1,1′-dimethyl-4,4′-bipyridinium).[226]

Iodomethane (**2**) was also emitted from fungi,[227] rice paddies,[228-233] and oat plants.[233]

3 Abiotic sources

3.1. Volcano

The early studies of volcanic gases and the presence of organoiodines were well documented.[2, 3, 8] A recent study of the volcanoes (Kuju, Satsuma Iwojima, Mt. Etna) has revealed an extraordinarily large array of organoiodines, including CH_3I, **2**,[234, 235] CH_2ClI **36**, and CH_3CH_2I **3**.[235]

3.2. Sediment and soils

The abiotic soil source could also produce CH_3I **2**.[236] Iodomethane **2** was emitted from wetlands[237] and peatlands.[238] Furthermore, presumed natural halogenation of humic material also occurred in Baltic Sea marine sediments leading to brominated and iodinated phenolic units in high molecular weight matter.[239]

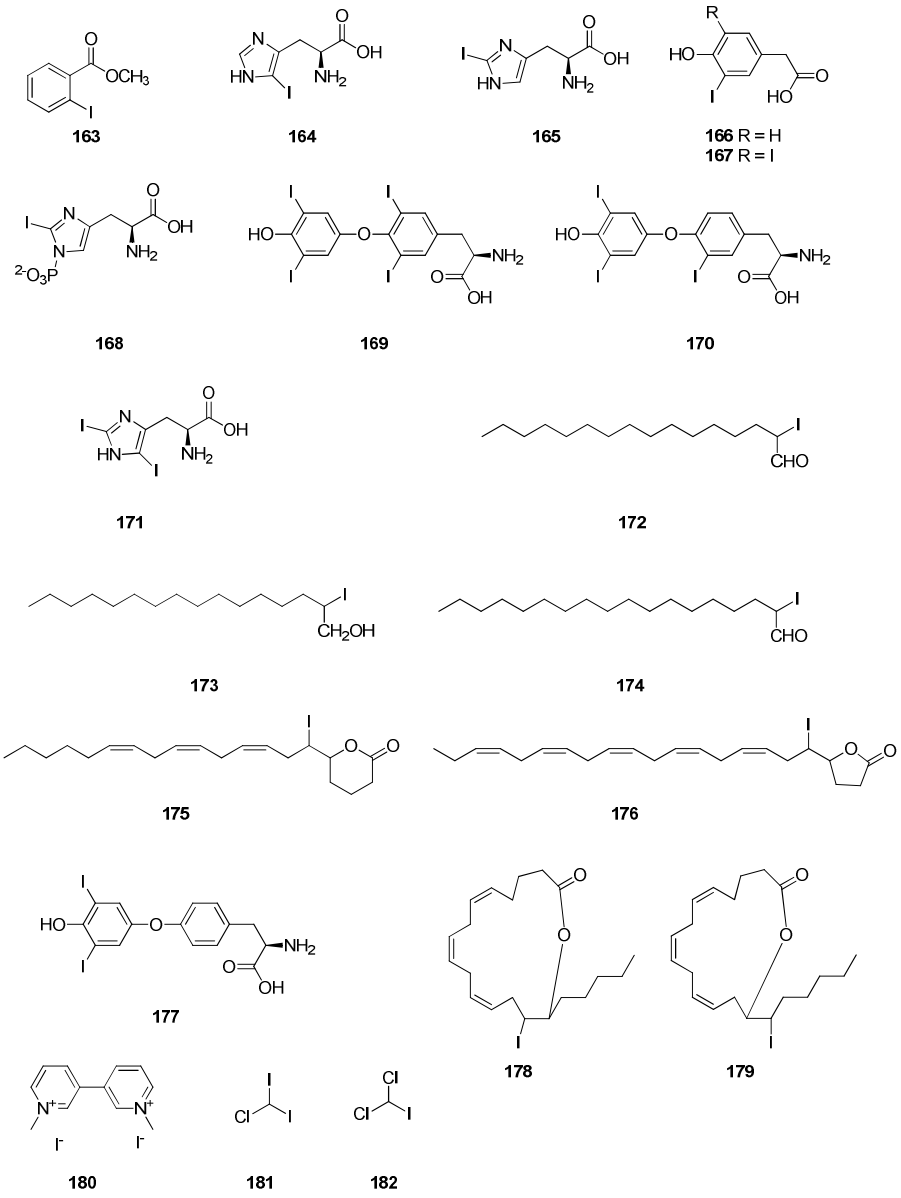
3.3. Atmosphere

CH_3I **2** was often detected in the oceanic atmosphere.[22-42] Diiodomethane **3** was a more significant source of iodine in the atmosphere than CH_3I **2**.[42]

3.4. Sea water

Iodomethane (CH_3I, **2**) has been detected in the oceans and in the air over oceans. Measurements indicated that the oceans were the major source of CH_3I **2**, and it has been observed that the concentration of CH_3I **2** was 1000 times higher in water near kelp (*Laminaria digitata*) beds than in the open ocean.

735 Volatile organoiodine compounds (VOIs) were the main carrier of iodine from the
736 oceans to the atmosphere. Sea-surface was the source of the short-lived VOIs. CH_2I_2 **3**,
737 $CHClI_2$ **181**, and CHI_3 **2** were identified in a series of laboratory experiments. The
738 VOIs were produced from the reaction of marine dissolved organic matter with
739 hypoiodous acid/molecular iodine, which were formed at the sea surface when ozone
740 reacted with dissolved iodide. The presence of dissolved iodide, dissolved organic
741 matter and ozone could lead to the sea-surface production of CH_2I_2 **3**, $CHClI_2$ **181**,
742 and CHI_3 **2**. As such, this process could provide a ubiquitous source of iodine to the
743 marine atmosphere.[240] Recent studies confirmed the oceanic presence of
744 chloroiodomethane (CH_2ClI, **36**),[31, 35-37, 39, 40, 42, 48-51, 53, 59, 241-244] bromoiodomethane
745 ($BrCH_2I$, **8**),[35, 37, 243] dibromoiodomethane ($CHBr_2I$, **5**),[243] and dichloroiodomethane
746 (Cl_2CHI, **182**).[243]



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748

749 **3.5. Miscellaneous**

750 Natural combustion sources such as biomass fires and other geothermal processes
751 accounted for a wide range of organohalogens. Biomass combustion also accounted
752 for some CH_3I **2**.[245-247]

753 **4 Biological significance**

754 More interesting was the possible biological significance of iodinated products.
755 The presence of iodine atoms in the compounds causes significant changes in the

physico-chemical characteristics, increasing their reactivity and changing the conformation of biological membranes. Novel natural iodinated products have been discovered and evaluated for their biological activity. It seems certain that some possess anticancer, antifungal and/or antibacterial properties. Halogens play an important role in natural processes, both biogenic and abiogenic. Recent studies have indicated a chemical defensive role for iodine containing metabolites in many marine invertebrates. Many marine and terrestrial organisms use organoiodines in chemical defense: feeding deterrents, irritants, or pesticides or in food gathering.[248] It seems clear that natural organoiodine compounds play an essential role in the survival of the organism, and the ability of the organism to synthesize such compounds for chemical defense and food gathering has evolved over time under the stress of natural selection.[249]

5 Halogenases and Biological halogenation

Nature has developed a series of exquisite methods to introduce halogens into organic compounds. Most of the enzymes are oxidative and require either hydrogen peroxide or molecular oxygen as a cosubstrate to generate a reactive halogens for catalysis.[250] For many years, the only known halogenases were the haloperoxidases, we now have a much better understanding of the enzymatic haologenation. Halogenated natural products are widely distributed in nature, some of them showing potent biological activities. Incorporation of halogen atoms in drug leads is a common strategy to modify molecules in order to vary their bioactivities and specificities. Chemical halogenation, however, often requires harsh reaction conditions and results in unwanted byproduct formation. It is thus of great interest to investigate the biosynthesis of halogenated natural products and the biotechnological potential of halogenating enzymes.[251]

A large and diverse series of halogenated natural products exist. In many of these compounds the halogen is important to biological activity and bioavailability. Enzymes capable of halogenating all kinds of different chemical groups from electron-rich to electron-poor, from aromatic to aliphatic have been characterized. Given that synthetic halogenation reactions are not trivial transformations and that halogenated molecules possess pharmaceutical usefulness, it will be worth investing into further research of halogenating enzymes.[252]

5.1. Haloperoxidases

The first halogenating microbial enzyme (fungal chloperoxidase) was discovered and described until 1959.[253] Haloperoxidases have been discovered in marine organisms, including Heme-Fe-vanadium haloperoxidase, and vanadium bromoperoxidases.[254]

5.1.1. Heme-containing haloperoxidases

The prototypical heme-dependent haloperoxidase is the fungal enzyme from *Caldariomyces fumago*.[255-257] Mammalian heme-dependent haloperoxidase are also known. In particular, a haloperoxidase in thyroid epithelial cells is responsible for a remarkable series of posttranslational oxidative modifications of tyrosyl residues in the protein thyroglobulin.[258] The reaction mechanism of heme-dependent haloperoxidase is likely to parallel that of haem enzymes.[259, 260] The halide ion is oxidized in the active site to ferric hypohalite by the ferryl-oxo species. This species in turn is generated through binding of hydrogen peroxide to the ferric resting state, which is followed by halide addition and finally release of the hypohalous acid.[252]

5.1.2. Vanadium-containing haloperoxidases

Vanadium-dependent haloperoxidases (V-HPOs) contain a vanadate prosthetic group and utilize hydrogen peroxide to oxidize a halide ion into a reactive

electrophilic intermediate. These metalloenzymes have a large distribution in nature, where they are present in macroalgae, fungi, and bacteria, but have been exclusively characterized in eukaryotes.[250] V-HPOs catalyze the oxidation of halides (chloride, bromide, and iodide) by hydrogen peroxide. Iodine uptake and the production of iodo-organic compounds by marine algae were thought to involve vanadium dependent iodoperoxidases. Iodoperoxidases catalyzed the oxidation of iodines, and they were named according to the most electronegative halide that they could oxidize, chloroperoxidases (CPOs) could catalyze the oxidation of chloride, as well as of bromide and iodide, bromoperoxidases (BPOs) react with bromide and iodide, whereas iodoperoxidases (IPOs) are specific of iodide.[261]

5.2. Flavin-dependent halogenases ($FADH_2$- dependent halogenases)

The understanding of enzymatic incorporation of halogen atoms into organic molecules has increased during the last few years.[262] Most known enzymatic halogenase reactions are oxidative, but more and more different strategies are being discovered in the marine environment. A novel type of halogenating enzymes, flavin-dependent halogenases, has been identified as a major player in the introduction of chloride and bromide into activated organic molecules. Flavin-dependent halogenases require the activity of a flavin reductase for the production of reduced flavin, required by the actual halogenase. A number of flavin-dependent tryptophan halogenases have been investigated in some detail, and the first three-dimensional structure of a member of this enzyme subfamily, tryptophan 7-halogenase, has been elucidated. This structure suggests a mechanism involving the formation of hypohalous acid, which is used inside the enzyme for regioselective halogenation of the respective substrate. The introduction of halogen atoms into non-activated alkyl groups is catalysed by non-heme Fe^{II} α-ketoglutarate-

and O_2-dependent halogenases. Examples for the use of flavin-dependent halogenases for the formation of novel halogenated compounds *in vitro* and *in vivo* reactions promise a bright future for the application of biological halogenation reactions.[263] Elucidation of the three-dimensional structure of $FADH_2$-dependent halogenases led to the understanding of the reaction mechanism, which involves the formation of hypohalous acids. Unactivated carbon atoms were found to be halogenated by nonheme iron, α-ketoglutarate- and O_2-dependent halogenases. The reaction mechanism of this type of halogenase was shown to involve the formation of a substrate radical.[264]

5.3. Non-heme Fe^{II}/α-ketoglutarate-dependent halogenases

Exploit a radical halogen species to allow halogenation of unactivated, aliphatic carbon centers. [252, 265] The Fe^{II} in halogenases is liganded by two histidine residues, α-ketoglutarate and chloride. An interesting aspect of α-ketoglutarate-dependent halogenases is the number of halogen transfers that can be carried out by one active site.

5.4. Methyl halide transferases

In this reaction mechanism, the halide reacts as a nucleophile with a SAM cofactor to displace *S*-adenosylhomocysteine.[266] whether this reaction is biologically relevant in the formation of methyl halides also remains to be shown.[267]

5.5. Biological Iodogenation

Several new enzymes capable of bioiodogenation have been identified. For example, one species of *Navicula* marine phytoplankton produced CH_2I_2 **3** and $ClCH_2I$ **36** *via* an iodoperoxidase (IPO), an enzyme capable of oxidizing iodide but not bromide or chloride.[35] A vanadium-dependent IPO has been purified and characterized from the brown alga *Saccorhiza polyschides*,[268] and also isolated from

the brown algae *Phyllariopsis brevipes*,[269] *Laminaria saccharina*, *L. hyperborea*, *L. ochroleuca*, and *Pelvetia canaliculata*.[270-272] One specific for the oxidation of iodide and another that could oxidize both iodide and bromide, were separated from the sporophytes of the brown alga *L. digitata* and purified to electrophoretic homogeneity.[261] Other studies of *L. digitata* and *L. saccharina* indicated the presence of IPO.[273-275] The marine microalga *Porphyridium purpureum*[276] and the alga *Ascophyllum nodosum*,[277] the Arctic green algae *Acrosiphonia sonderi* and *Enteromorpha compressa* have high IPO activity.[274] Two peroxidase enzymes[278] that catalyze the iodination of tyrosine were horseradish peroxidase (HRP) and lactoperoxidase (LPO).[279] The latter enzyme was dominant for the iodination of tyrosine in mammals. A recent study analyzing gene expression in the brown alga *Laminaria digitata* has shed light on how V-BrPOs and vanadium-dependent iodoperoxidases are up-regulated upon defense elicitation.[280] Vanadium-dependent iodoperoxidases in *Laminaria digitata*, a novel biochemical function diverged from brown algal bromoperoxidases.[281]

An electrifying development was the utilization of the halide/peroxidase/hydrogen peroxide chemical system by humans and other mammals to generate active halogen (HOCl and HOBr) in order to destroy microorganisms. Thus, human white blood cells (eosinophils and neutrophils) contained myeloperoxidase, which, in the presence of chloride, bromide, or iodide, and hydrogen peroxide, rapidly form active halogen, resulting in the death of bacteria and fungi, and even tumor cells, by halogenation reactions,[282-284] it would appear that biohalogenation was an integral component of our immune system.

Simple halogen substituents frequently afford key structural features that account for the potency and selectivity of natural products, including antibiotics and hormones.

For example, when a single chlorine atom on the antibiotic vancomycin is replaced by hydrogen, the resulting antibacterial activity decreases by up to 70%. This Account analyzes how structure underlies mechanism in halogenases, the molecular machines designed by nature to incorporate halogens into diverse substrates.

Structural characterization has provided a basis toward a mechanistic understanding of the specificity and chemistry of these enzymes. In particular, the latest crystallographic snapshots of active site architecture and halide binding sites have provided key insights into enzyme catalysis. A thorough mechanistic analysis will elucidate the biological principles that dictate specificity, and the application of those principles to new synthetic techniques will expand the utility of halogenations in small-molecule development.[285]

6 Conclusion

The few examples of iodine containing natural products could be grouped into five main structural classes: 1) volatile compounds having very short carbon frameworks; 2) nucleoside derivatives; 3) amino acid (tyrosine, tryptophan, and histidine) derivatives; 4) fatty acid derivatives; and 5) terpenoid derivatives. Of all iodinated compounds, most of them (159/182) were derived from marine sources (especially marine algae, sponges, and corals).

But what was on the base of the existence for natural organoiodines? Some organoiodines function as recyclers of iodines, as pheromones and hormones,[193] as chemical defence substances: such as antimicrobials,[58] anti-UVs,[87] antifeedants,[134, 153] and antifoulants.[132] The benefit to mankind was that many organoiodines displayed enormous biological activity that may lead to clinical drugs. Indeed, most of these promising compounds were heterocycles.[8] There are many examples of the positive, beneficial effects of halogen substitution on organic compounds, and excellent

reviews on this topic were available.[286] An iodinated enediyne antibiotic CLM γ_1^I (**161**) was twice more active than the brominated analog CLM γ_1^{Br}.[287] Likewise, iodine-substituted gomisin J derivatives were more effective than the natural product itself as HIV-1 reverse transcriptase inhibitors.[288] The geodiamolide D **81** (iodinated) induced microfilament disruptions and was thrice more effective than geodiamolide E (brominated counterpart).[101] Geodiamolide H **83** showed *in vitro* cytotoxicity against a number of human cancer cell lines. Surprisingly, geodiamolide I (brominated counterpart) was completely devoid of activity.[106] Iodovulone II **108** showed significant cytotoxic activity against MOLT-4, DLD-1, and IMR-90 cells. While its brominated and chlorinated counterparts showed no activities.[128] Hicksoanes A-C **130-133** showed antifeeding activity against goldfish, hicksoane C **133** having two atoms of iodine had a higher activity than its counterparts hicksoanes A **131** and B **132** having one atom of iodine. As shown in the literature,[289] halogenation increased the antifeeding activity. Iodine substitution on aromatic rings greatly stabilized cross-strand aromatic rings in model β-hairpin peptides,[290] which was proved by interaction between the thyroid hormone 3,5,3′-triiodothyronine **166**, thyroxine **169**, and the thyroid hormone receptor.

Iodogenating enzymes have been identified for the biosynthesis of iodogenated compounds by catalyzing the formation of carbon-iodine bond. The biological importance of iodogenating enzymes in bioiodogenation has aroused wide concern. Meanwhile, using modern biotechnology, for example, combinatorial biosynthesis and directed evolution, the prospects for generating iodinated derivatives of valuable natural products would therefore appear very promising.

Traditional synthetic methods of integrating halogens into complex molecules are often complicated by a lack of specificity and regioselectivity. Nature, however, has

developed a variety of elegant mechanisms for halogenating specific substrates with both regio- and stereoselectivity. An improved understanding of the biological routes toward halogenation could lead to the development of novel synthetic methods for the creation of new compounds with enhanced functions. While chemical synthesis of organohalogens can be difficult, the biological production of these compounds occurs under relatively mild conditions and often with a greater degree of specificity. Therefore an understanding of the biosynthesis of halometabolites, and in particular, the enzymology of carbon-halogen bond formation, may provide convenient biotechnological methods for the halogenation of organic compounds.[124] Biological halogenation can provide this specifity and selectivity. But the technology transfer to large scale manufacturing and established industrial methods are yet to be realized.

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ABBREVIATIONS

AML	acute myeloid leukemia
BPO	bromoperoxidase
CLM	calicheamicin
CPO	chloroperoxidase
DIT	3,5-diiodotyrosine
DPPA	diphenyl phosphorazidate

HRP	horseradish peroxidase
2-IHDA	2-iodohexadecanal
2-IHDO	2-iodohexadecan-1-ol
IPO	iodoperoxidase
LPO	lactoperoxidase
MIT	monoiodotyrosine
MIH	monoiodohistidine
MPO	myeloperoxidase
PIH	phosphoriodohistidine
PKSs	polyketide synthases
T4	thyroxine
T3	3,5,3′-triiodothyronine
TPO	thyroid peroxidase
UV	ultraviolet
VOIs	volatile organoiodine compounds

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