Aurilide Family

Subjects: Chemistry, Organic | Others

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Aurilides are a class of depsipeptides occurring mainly in marine cyanobacteria. Members of the aurilide family have shown to exhibit strong cytotoxicity against various cancer cell lines. These compounds bear a pentapeptide, a polyketide, and an α-hydroxy ester subunit in their structure.

marine drugs aurilides depsipeptides

1. Introduction

Since the late 1960s, marine organisms have been intensively explored as hopeful resources for anticancer drugs, and a diverse array of new compounds are still being discovered every year. In particular, the sea hare *Dolabella auricularia* is known as a prolific producer of cytotoxic and/or antitumor structurally unique secondary metabolites such as dolastatins 10 and 15 [1]. From a specimen of this marine organism collected in the Japanese sea, Suenaga et al. [2] isolated in 1996 aurilide (**1**), a 26-membered cyclodepsipeptide, which exhibits a strong cytotoxicity against HeLa S_3 cells with an IC_{50} of 0.011 μg/mL.

In the next two decades, the aurilide family expanded with the discovery of ten new members, which were structurally analogous to aurilide (structures of this family are shown in Figure 1).

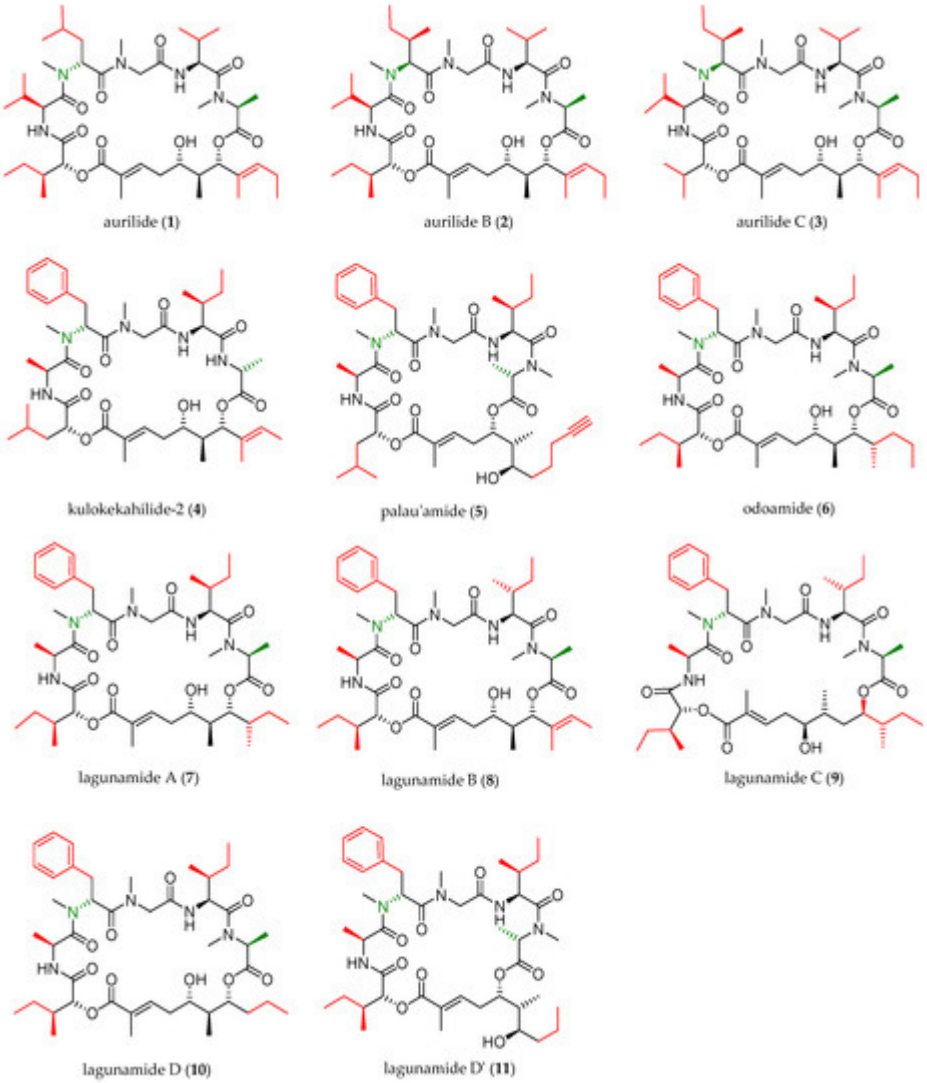


Figure 1. Aurilide family members.

As shown in Table 1, cyanobacterium *Lyngbya majuscule* was the source of aurilide B (**2**) and C (**3**), and cephalaspidean mollusc *Philinopsis speciosa* furnished kulokekahilide-2 (**4**). Palau'amide (**5**), odoamide (**6**), and lagunamides A (**7**), B (**8**), C (**9**), D (**10**), and D' (**11**) were isolated from different sources of marine cyanobacteria.

Table 1. Marine sources of the aurilide family members.

Aurilide-Family Member	Year of Isolation	Marine Source	Collection Site
aurilide (**1**)	1996 [2]	sea hare *Dolabella auricularia*	Japanese sea
aurilide B (**2**)	2006 [3]	cyanobacterium *Lyngbya majuscula*	Papua New Guinea
aurilide C (**3**)	2006 [3]	cyanobacterium *Lyngbya majuscula*	Papua New Guinea
kulokekahilide-2 (**4**)	2004 [4]	cephalaspidean Mollusk*Philinopsis speciosa*	

Aurilide-Family Member	Year of Isolation	Marine Source	Collection Site
palau'amide (**5**)	2000 [5]	cyanobacterium *Lyngbya* (Oscillatoriaceae)	Ulong Channel, Palau
odoamide (**6**)	2016 [6]	cyanobacterium *Okeania* sp.	Japanese sea
lagunamide A (**7**)	2010 [7]	cyanobacterium *Lyngbya majuscula*	western lagoon of Pulau Hantu Besar, Singapore
lagunamide B (**8**)	2010 [7]	cyanobacterium *Lyngbya majuscula*	western lagoon of Pulau Hantu Besar, Singapore
lagunamide C (**9**)	2011 [8]	cyanobacterium *Lyngbya majuscula*	western lagoon of Pulau Hantu Besar, Singapore
lagunamide D (**10**) and D'(**11**)	2019 [9]	collection of marine cyanobacteria (a mixture of *Dichothrix* sp. and *Lyngbya*sp. in a ratio of 1:1 with minor amount of *Rivularia* sp. present)	Loggerhead Key in the Dry Tortugas in Florida

Since the first synthesis of aurilide in 1996 by Suenaga and co-workers [2], the aurilide family has attracted considerable attention from the synthetic community due to potent antiproliferative activity as well as synthetically challenging molecular architecture and additional total syntheses of aurilide and other members of the aurilide class have been reported.

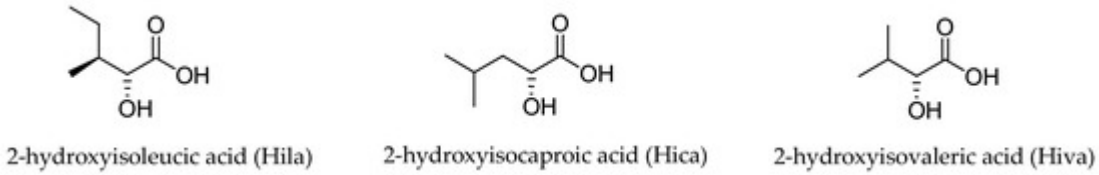
2. Structural Features

Structurally, the aurilide family members can be described as cyclic depsipeptides, whose framework can be divided into three subunits: an α-hydroxy acid residue, a polyketide segment containing three or four stereogenic centers, and a pentapeptide.

The size of the macrocycle differs slightly; eight of them (**1**–**4**, **6**–**8** and **10**) are 26-membered rings, and lagunamide C (**9**) is a 27-membered ring, while plau'amide (**5**) and lagunamide D' (**11**) are 24-membered rings.

2.1. Differences in the α-Hydroxy Acid and the Polyketide Subunits

Three different α-hydroxy acids (Figure 2) can be found in the macrocyclic structure of the aurilide family members. 2-Hydroxyisoleucic acid (Hila) is the most common residue and can be found in aurilide (**1**), aurilide B (**2**), lagunamides A (**7**), B (**8**), C (**9**), D (**10**), and D' (**11**) and odoamide (**6**). Kulokekahilide-2 (**4**) and palau'amide (**5**) bear a 2-hydroxyisocaproic acid (Hica), whereas 2-hydroxyisovaleric acid (Hiva) is exclusive to aurilide C (**3**).



2-hydroxyisoleucic acid (Hila) 2-hydroxyisocaproic acid (Hica) 2-hydroxyisovaleric acid (Hiva)

Figure 2. The three α-hydroxy acids present in the structure of the aurilide family members.

The polyketide subunit consists of an α,β-unsaturated 5,7-dihydroxy acid bearing three contiguous stereocenters at C5, C6, and C7 with the relative configuration 5,6- and 6,7- *anti* and an aliphatic saturated or unsaturated side-chain at C8, whose nature is depending on the member of the family (Figure 3). Odoamide (**6**) and lagunamide A (**7**) bear a fourth stereocenter in the side chain, whose absolute configuration is *R* for the first compound and *S* for the second one. Lagunamide C (**9**) can be considered as a subclass of aurilide-related compounds that has a ring expansion due to the additional methylene carbon inserted in the polyketide-derived moiety at C7.

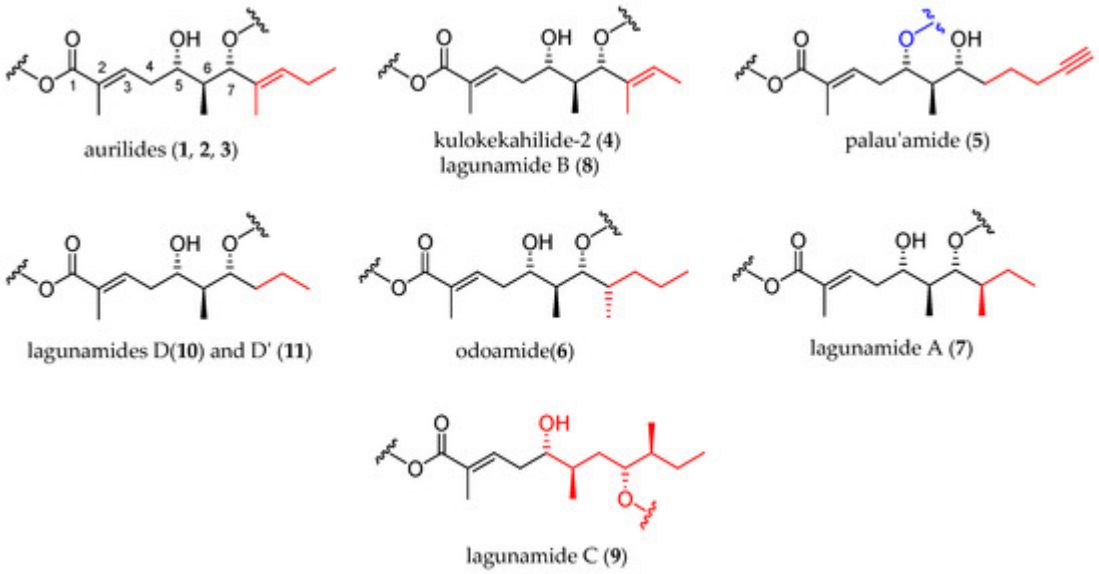
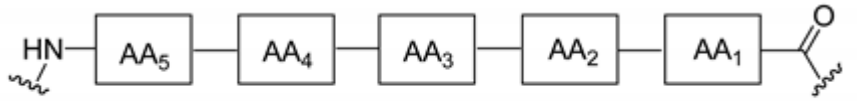


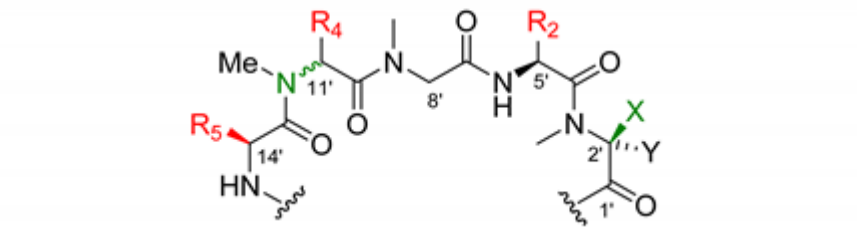
Figure 3. Polyketide moieties of the aurilide family members.

2.2. Differences in the Pentapeptide Fragment

Most of the depsipeptides of the aurilide class share similar peptide substructures. However, some of them have unique structural motifs and particularly in aurilides, three of the amino acids have different side chains. The first amino acid (AA_1, Table 2) is l-*N*-methylalanine with the sole exception of kulokekalide-2 (**4**) in whose structure the other enantiomer is present. The third amino acid (AA_3) is in all cases sarcosine, and the fifth one (AA_5) is l-alanine, except for aurilides (**1**–**3**), which bear an l-valine. The main differences concern the second and fourth amino acid. Concerning the second amino acid (AA_2), l-valine is exclusive to aurilides (**1**–**3**), while l-isoleucine is present in the other members of the family, although the absolute configuration of the side-chain stereocenter is not always the same (usually *S* but *R* in two cases). The fourth amino acid (AA_4) normally found is d-phenylalanine, but in the case of aurilide (**1**), AA_4 is replaced by l-leucine and in aurilides B (**2**) and C (**3**), it is replaced by d-isoleucine.

Table 2. Pentapeptide side chains in the different members of the aurilide family.





	R_5	R_4	R_2	C11′ Configuration	X	Y
Aurilide (**1**)	*i*-Pr	*i*-Bu	*i*-Pr	R	Me	H
Aurilide B (**2**)	*i*-Pr	(*R*)-*sec*-butyl	*i*-Pr	S	Me	H
Aurilide C (**3**)	*i*-Pr	(*R*)-*sec*-butyl	*i*-Pr	S	Me	H
Kulokekahilide-2 (**4**)	Me	Bn	(*S*)-*sec*-butyl	R	H	Me
Palau'amide (**5**)	Me	Bn	(*S*)-*sec*-butyl	R	Me	H
Odoamide (**6**)	Me	Bn	(*S*)-*sec*-butyl	R	Me	H
Lagunamide A (**7**)	Me	Bn	(*S*)-*sec*-butyl	R	Me	H
Lagunamide B (**8**)	Me	Bn	(*R*)-*sec*-butyl	R	Me	H
Lagunamide C (**9**)	Me	Bn	(*R*)-*sec*-butyl	R	Me	H
Lagunamide D (**10**)	Me	Bn	(*S*)-*sec*-butyl	R	Me	H
Lagunamide D' (**11**)	Me	Bn	(*S*)-*sec*-butyl	R	Me	H

	$HeLaS_3$	P388	BJ	BJ Shp 53	PC 3	SK-OV-3	HCT8	NCI-H460	Neuro-2a *	MDA-MB-435	A-10	KB	A549
Aurilide (**1**) [2]	11												
Aurilide B (**2**) [3]								10	40				
Aurilide C (**3**) [3]								50	130				
Kulokekalide-2 (**4**) [4]		4.2				7.5				14.6	59.1		
Palau'amide (**5**) [5]												13	
Odoamide (**6**)	26.3												4.2

	HeLaS$_3$	P388	BJ	BJ Shp 53	PC 3	SK-OV-3	HCT8	NCI-H460	Neuro-2a *	MDA-MB-435	A-10	KB	A549
[6][10]													
Lagunamide A (**7**) [7][11]		6.4	20.2	58.8	2.5	3.8	1.6						2.9
Lagunamide B (**8**) [7][11]		20.5					5.2						
Lagunamide C (**9**) [8]		24.4			2.6	4.5	2.1						2.4
Lagunamide D (**10**) [9]													7.1
Lagunamide D'(**11**) [9]													68.2

ndria [12]. ochondria inner membrane protein, which in turn activates the proteolytic processing of optic atrophy 1 (OPA1), leading to mitochondrial fragmentation and apoptosis [13].

Lagunamide A induces caspase-mediated mitochondrial apoptosis in A549 cells [14]. Indeed, lagunamide A causes mitochondrial dysfunction followed by cell death along with the dissipation of mitochondrial membrane potential (Δφm) and overproduction of reactive oxygen species (ROS). It was proved that both anti- and pro-apoptotic B-cell lymphoma 2 (Bcl-2) family proteins, especially myeloid cell leukemia-1 (Mcl-1), participated in lagunamide A-induced mitochondrial apoptosis. The overexpression of Mcl-1 partly rescued A549 cells from lagunamide A-induced apoptosis.

Moreover, lagunamides A (**7**), B (**8**), and C (**9**) displayed significant antimalarial properties, with IC_{50} values of 0.19, 0.91, and 0.29 μM, respectively, when tested against *Plasmodium falciparum* [7].

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