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Antitumor Acetylenic Lipids

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ABSTRACT

This article describes antitumor acetylenic lipids and related compounds obtained from living organisms. Acetylenic lipids belong to a class of molecules containing triple bond(s). They are found in algae, plants, fungi, microorganisms, and marine invertebrates. Although polyacetylenes are common as components of terrestrial plants, fungi, and bacteria, it is only within the last 50 years that biologically active polyacetylenes having unusual structural features have been reported from plants, cyanobacteria, algae, invertebrates, and other sources. Naturally occurring aquatic acetylenes are of particular interest since many of them display important biological activities and possess antitumor, antibacterial, antimicrobial, anti-fungal, HIV inhibitory and immunosuppressive properties. There is no doubt that they are of great interest, especially for the medical, pharmacological, medicinal chemistry, and/or pharmaceutical industries. This review presents structures and describes cytotoxic activities of more than 90 acetylenic lipids, including fatty acids, glycerides, sterols and carotenoids isolated from living organisms.

KEYWORDS

Acetylenic; Polyacetylenes, Antitumor; Sterols; Carotenoids; Fatty Acids; Lipids.

INTRODUCTION

Natural acetylenic and/or polyacetylenic metabolites have been isolated from a wide variety of plants, fungal species, and marine algae and invertebrates [1-10]. Many of them display important biological activities, namely antitumor, antibacterial, antimicrobial, antifungal, and other chemical and medicinal properties [11-14]. More than 1000 acetylenic metabolites have been isolated and identified from plants, fungi, micro-organisms, and other organisms [1-5,11,12,15-20].

Naturally occurring acetylenic lipids possessing an acetylenic unit, as well as polyacetylenes, are of particular interest as many of them display important biological activities, namely antitumor, antibacterial, antimicrobial, antifungal, and others. This paper describes acetylenic antitumor lipids that are deemed as naturally occurring.

Acetylenic Fatty Acids and Glycerides

The antitumor acetylenic compounds 2-*cis*-dehydro-matricaria acid (**1**), 2-*trans*-dehydromatricaria acid (**2**), *cis*-dehydromatricaria Me ester (**3**), and *trans*-dehydromatricaria Me ester (**4**) were obtained from roots of *Solidago virga-aurea* (Compositae) [21,22], and also from other species [23-26].

Polyacetylene (-)-17-hydroxy-9,11,13,15-octadeca-tetraynoic acid (**5**), referred to as minquartynoic acid, from *M. guianensis* stem bark showed cytotoxic activity against P-388 murine lymphocytic leukemia *in vitro*. The P-388 ED_{50} of the pure compound was 0.2 µg/mL, and it was also active in the brine shrimp larvicidal bioassay with an LC_{50} of 5 µg/mL.

These biological activities could account for the alleged efficacy of the plant in folk usage [27,28]. More recently, minquartynoic acid was isolated from the air-dried bark of *Coula edulis,* the twigs of *Ochanostachys amentacea* (both plants belonging to the Olacaceae), and from *Minquartia guianensis* bark [29-32]. In addition, acetylenic acids (**6** and **7**) were isolated from the twigs of *Ochanostachys amentacea* [31,32], and their cytotoxic activities determined (Table 1).

Minquartynoic acid (**5**) also showed moderate *in vitro* activity against *Plasmodium falciparum* and *Leishmania major*, and strongly inhibited phytohaemagglutinin A - induced proliferation of human lymphocytes [33].

Three acetylenic acids: octadeca-8,10-diynoic (**8**), (*Z*)-octadec-12-ene-8,10-diynoic (**9**), and octadeca-8,10,12-triynoic (**10**) acids were isolated from aqueous acetone extracts of stems and leaves. All compounds showed inhibitory activity against cancer cell invasion (MM1) *in vitro* (Table 2) [34,35]. Five C_{16}-acetylenic fatty acids, hexadec-8-ynoic acid (**11**), hexadec-10-ynoic acid (**12**), hexadeca-8,10-diynoic (**13**), hexadeca-6,8,10-trienoic (**14**), and hexadeca-8,10,12-triynoic (**15**) acids were prepared and their inhibitory activity against cancer cell invasion examined [36].

1 2-*cis*-Dehydromatricaria acid, R = H
2 2-*trans*-Dehydromatricaria acid, R = H
3 *cis*-Dehydromatricaria ester, R = Me
4 *trans*-Dehydromatricaria ester, R = Me

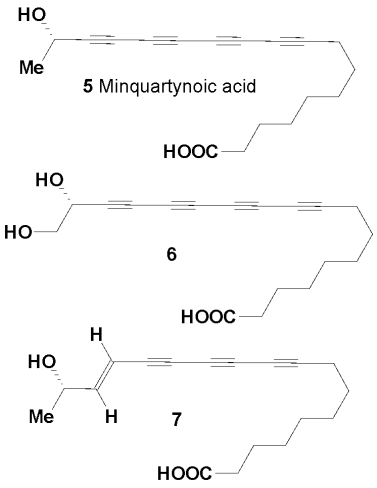
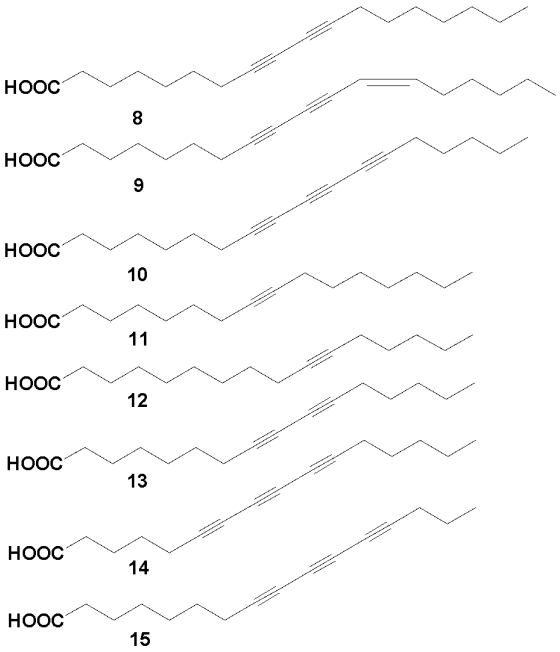


Table 1. Cytotoxic activity for compounds (**1-7**) (ED_{50}, μg/mL).

Cell lines	5	6	7
BC1	3.5	> 20	> 20
Lu1	4.1	14.6	> 20
Col2	5.5	> 20	9.9
KB	3.7	2.6	1.1
KB-V+	2.8	11.9	> 20
KB-V-	4.3	13.4	> 20
LNCaP	1.6	9.2	0.30
SW626	4.1	19.4	0.36
SKNSH	1.4	6.7	3.7
M109	3.7	10.1	5.4

Key to cell lines used: BC1, human breast cancer; Lu1, human lung cancer; Col2, human colon cancer; KB, human oral epidermoid carcinoma; KB-V+, multidrug-resistant KB assessed in the presence of vinblastine (1 μg/mL); KB-V-, multidrug-resistant KB assessed in the absence of vinblastine; LNCaP, hormone-dependent human prostate cancer; SW626, human ovarian cancer; SKNSH, human neuroblastoma cancer; M109, mouse lung cancer.

The results indicated that the origin C_{18}-triyne fatty acid (**10**) and the synthetic C_{16}-triyne fatty acids (**14** and **15**) inhibit cancer cell invasion in spite of their simple chemical structures.



Three acetylenic metabolites (**16**-**18**) were isolated from the sponge *Stelletta* sp. collected from Gagu-Do, Korea [37]. These compounds exhibited no significant antimicrobial activity and displayed only weak cytotoxicity against the human leukemia cell-line K562 with LC_{50} values of 43, 51, and 62 μg/mL for (**16**-**18**), respectively.

The acetylenic acid (**19**) and its methyl ester (**20**) were isolated from the sponge *Xestospongia muta*. The EDs of **19** for 50% inhibition *in vivo* PS and L1210 cell culture evaluations were 24 and 34 μg/mL, respectively, and the corresponding doses of **20** were 29 and 34 μg/mL [38]. Similar brominated fatty acids (**21** and **22**) were isolated from an Indonesian sponge, *Oceanapia* sp. [39]. Their common structural feature is a (13*E*, 15*Z*)-14,16-dibromodiene terminus. Both compounds are unstable oils. The mixture exhibits mild cytotoxicity towards KB cells. A methanol-soluble extract of the frozen marine sponge *Petrosia* sp. showed significant activity in the brine shrimp larvae lethality bioassay (LD_{50} 30 μg/mL), and showed cytotoxic activities against a panel of human solid-tumor cells.

Twelve brominated acetylenic acids, (**23a-d**, **24a-d**, and **25**), together with the known compound (**26**) were isolated from marine sponge *Xestospongia testudinaria* (Nepheliospongiidae) [40]. All isolated brominated acetylenic acids showed weak cytotoxicity against the tumor cell lines HeLa, and HL-60. Pellynic acid (**27**) inhibited inosine monophosphate dehydrogenase with an IC_{50} of 1 pM/mL [41].

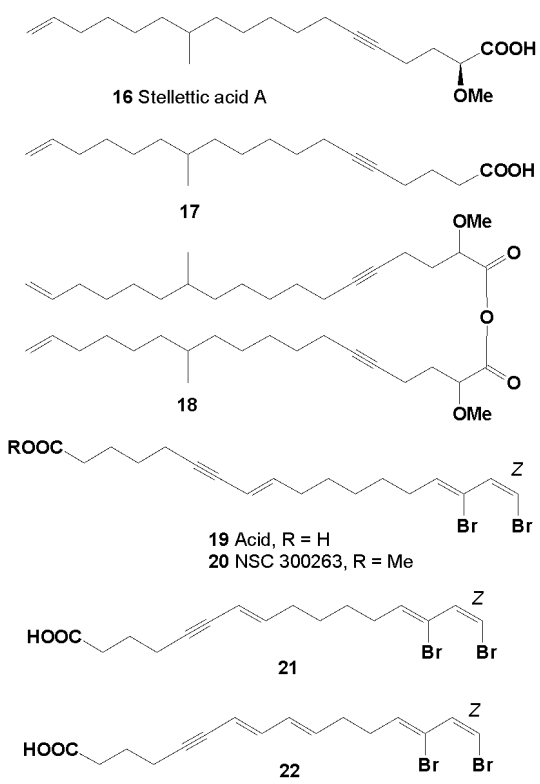


Table 2: Inhibitory activities of C_{16} and C_{18}-acetylenic acids on cancer cell invasion (MM1).

Compound	Concentration (μg/mL)	Inhibitory activity (%)
8	10	61.1
9	10	89.8
10	10	99.4
10	5	94.9
10	2.5	45.6
11	10	82.4
12	10	77.2
13	10	85.6
14	10	95.7
14	5	85.4
14	2.5	50.3
15	10	98.7
15	5	90.7
15	2.5	60.5

Montiporic acids A and B were not only antibacterial against *Escherichia coli*, but also cytotoxic activities against P-388 murine leukemia cells, with IC_{50} values of 5 and 12 μg/mL, respectively. Cytotoxic activity of compounds **29**, **30**, **32** and **33** showed in Table 3.

Many species of tunicata produce bioactive compounds [42]. Callysponginol sulfate A (**35**), a sulfated C_{24} acetylenic fatty acid from the marine sponge *Callyspongia truncata*, is a membrane type 1 matrix metalloproteinase (MT1-MMP) inhibitor. Compound **35** inhibited MT1-MMP with an IC_{50} value of 15 μg/mL, and sodium 1-(12-hydroxy)-octadecanyl sulfate was isolated from a marine tunicate as a matrix metalloproteinase 2 (MMP2) inhibitor [43,44]. This compound inhibited MMP2 with an IC_{50} value of 9.0 μg/mL.

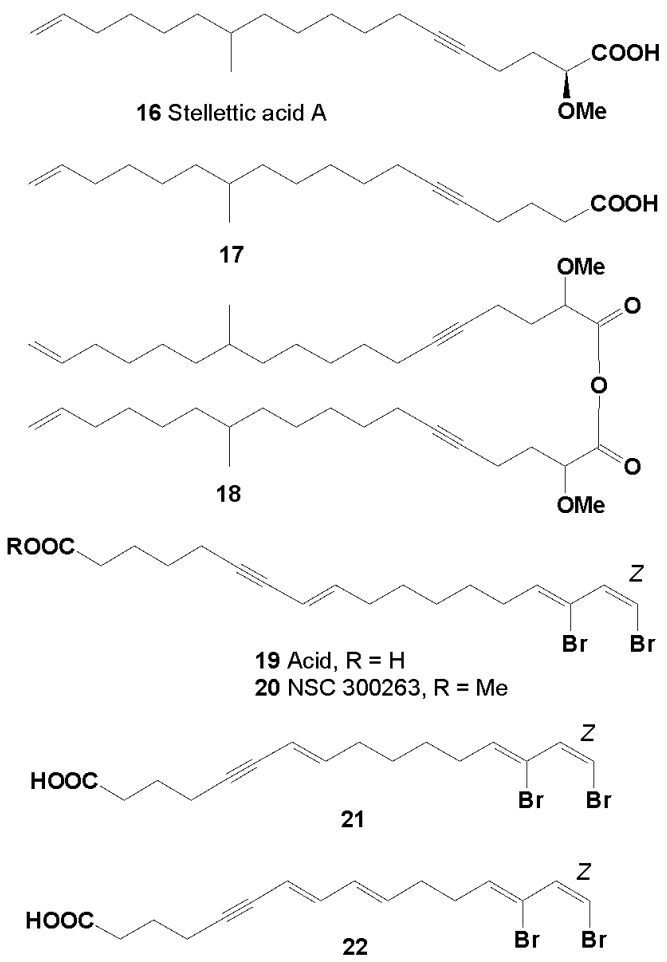


Table 3. Cytotoxic activities (ED_{50} μg/mL) of compounds against human solid tumor cells.

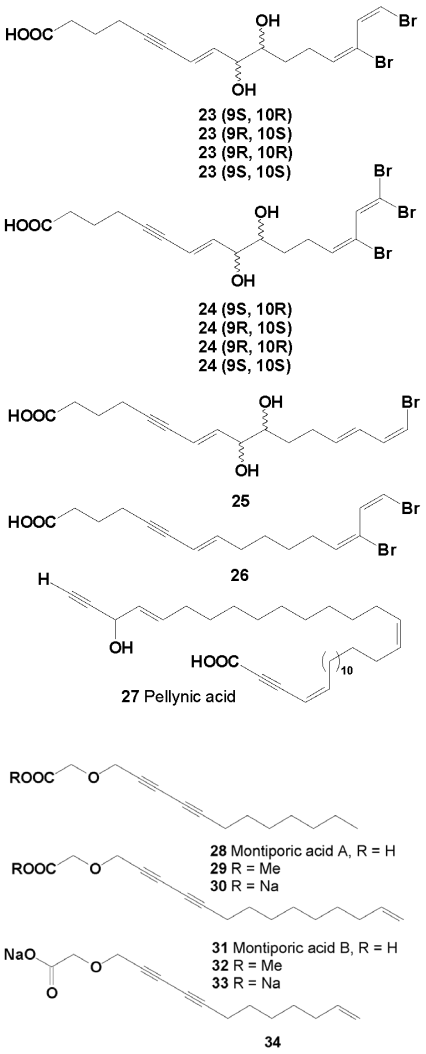
Compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
29	> 30	20.52	> 30	> 30	25.61
30	> 30	> 30	> 30	> 30	> 30
32	> 30	> 30	> 30	> 30	> 30
33	6.31	7.50	7.97	7.72	8.30
34	> 30	20.52	> 30	> 30	25.61

Key to cell lines used: A549 = human lung cancer;

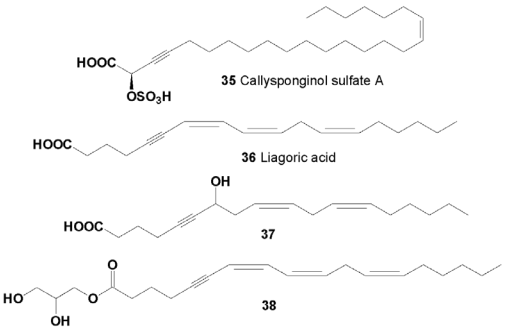
SK-OV-3 = human ovarian cancer; SK-MEL-2 = human skin cancer;

XF498 = human CNS cancer; HCT15 = human colon cancer.

The genus *Montipora* (phylum *Cnidaria*) is very rich in acetylenic compounds and many of them were shown to be cytotoxic and/or to possess antifungal and antibacterial properties. Two polyacetylene carboxylic acids, montiporic acids A (**28**) and B (**31**), have been isolated from the eggs of the scleractinian coral *M. digitata* [45]. They exhibited antimicrobial activity against *Escherichia coli* and cytotoxicity towards P-388 murine leukemia cells (Table 3).



The structures of octadec-5-yne-7*Z*,9*Z*,12*Z*-trienoic acid (liagoric acid) (**36**), 7-hydroxy-octadec-5-yne-9*Z*,12*Z*-dienoic acid (**37**), and glyceryl octadec-5-yne-7*Z*,9*Z*,12*Z*-trienoate (**38**) isolated from *Liagora farinosa* are presented below. These compounds showed acute toxicity toward *Eupomacentrus leucostictus* at concentrations from 5 to 8 µg/mL. It was shown that at a concentration of 31 µM, liagoric acid inhibited cyclooxygenase activity [46,47].



The extract obtained from the leaves of *Anacolosa pervilleana* was selected for its significant activity in assays. One new (*E*)-tridec-2-en-4-ynedioic acid named anacolosine (**39**), together with three known acetylenic acids, the octadeca-9,11,13-triynoic acid (**40**), (13*E*)-octadec-13-en-9,11-diynoic acid (**41**), (13*E*)-octadec-13-en-11-ynoic acid (**42**) were isolated from the leaves and showed anti-metabolic and antiviral activites (Table 4) [48].

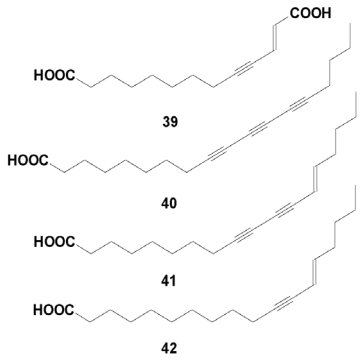
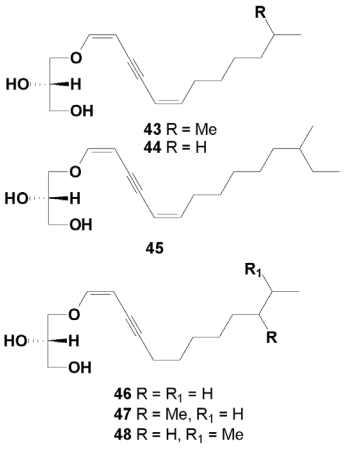


Table 4. Anti-metabolic and antiviral activities of compounds (**39**-**42**) in Vero cells against CHIKV, and in a DENV RdRp and WNV RdRp assay (µM).

Cell lines	39	40	41	42
Vero cells (CC_{50}) cells cecells	> 420	> 420	2.5	19.3
CHIKV (EC_{50})	30	> 30	2.7	25
DENV RdRp (IC_{50})	23	> 23	2.2	10.5
WNV RdRp (IC_{50})	30	> 30	2.7	12.7

Acetylenic enol ethers of glycerols, including bioactive glycerolipids (**43-48**)**,** have been isolated from a sponge of the genus *Petrosia*. Compounds **1** and **3** exhibited weak cytotoxicity against a human leukemia cell-line (K-562) [49]. Bioactivities of glyceryl enol ether compounds (**43, 44** and **46**), of the yne-diene series, exhibited weak cytotoxicity against the human leukemia cell-line K-562 (LC_{50} 9, 57, 29 µg/mL, for (**43, 44** and **45**, respectively), while (**46-48**), possessing the yne-ene group, were less active (LC_{50} > 100 µg/mL).



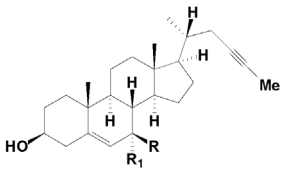
Antitumor Sterols and Derivatives

A few species of acetylenic sterols have been discovered, and tested on anticancer activity. Acetylenic sterols, gelliusterol A (26,27-bisnorcholest-5-en-23-yn-3β,7α-diol), its corresponding 7-ketone, gelliusterol B (26,27-bisnorcholest-5-en-23-yn-

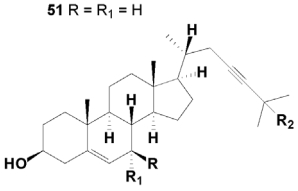
3β-ol-7-one), and gelliusterols C (cholest-5-en-23-yn-3 β-7-one) and D (cholest-5-en-23-yn-3β,25-diol-7-one), were isolated from an unidentified species of sponge, *Gellius* sp. [50].

Biological evaluation of gelliusterols A (**49**), B (**50**), and C (**52**) was performed on cancer cell lines P-388, HT-29, A-549, DU-145, and MEL-28. Gelliusterols A and B exhibited moderate activity, with IC_{50} values greater than 1 µg/mL. An activity of 0.5 µg/mL was observed with gelliusterol C against HT-29, while the other cell lines gave IC_{50} values above 1 µg/mL. The quantity of gelliusterol D (**53**) and cholest-5-en-23-yn-3β-ol (**68**) was insufficient for biological testing [50-52]. Steroids containing an atypical acetylenic unit as a component of the side chain have been obtained from extracts of the sponge *Calyx nacaaensis*, where 26,27-bisnorcholest-5-en-23-yn-3β-ol (**51**) and (**54**) were minor components [51].

A few acetylenic phytosterols were found in plant species. The first acetylenic sterols (**55**-**59**) from *Gymnostemma pentaphyllum* were isolated by Akihisa and co-workers in 1989 [53]. *G. pentaphyllum* belongs to the Cucurbitaceae family, which is widely distributed in the south of the Qinling Mountains and the Yangtze River in China. *G. pentaphyllum* is rich in sterols, gypenosides, polysaccharides and flavonoids.

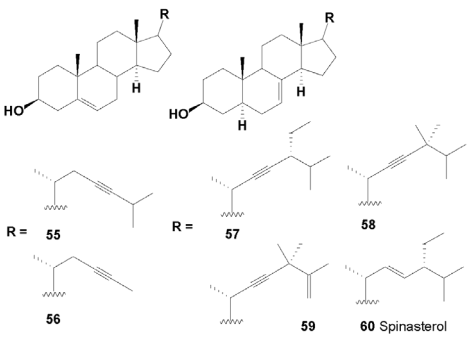


49 Gelliusterol A, R = H, R_1 = OH
50 Gelliusterol B, R,R_1 = O
51 R = R_1 = H



52 Gelliusterol C, R, R_1 = O, R_2 = H
53 Gelliusterol D, R,R_1 = O, R_2 = OH
54 R = R_1 = R_2 = H

These components have various activities including antitumor, cholesterol-lowering and hypoglycemic activities, anti-aging, anti-inflammatory, and cardiovascular effects [54-57]. Compounds (**55** and **56**) have similar structures to gelliusterols.

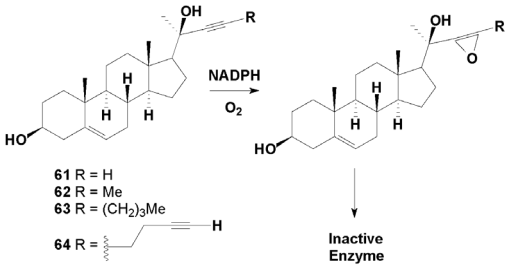


R = **55**, **56**; R = **57**, **58**, **59**, **60** Spinasterol

Acetylenic sterols having the same structure (except for the side chains) as the anticancer agent spinasterol (**60**) were isolated from *Pueraria* root (*Pueraria mirifica* from Thailand and *Pueraria lobata* from Korea) [58]. These plants are used as a rejuvenating folk medicine in Thailand and China. The ethanol extracts had significant antiproliferative effects on breast cancer cell lines, including MCF-7, ZR-75-1, MDA-MB-231, SK-BR-3, and Hs578T.

Spinasterol inhibited the growth of some breast cancer cell lines (MCF-7, MDA-MB-231) in a dose- and time dependent manner, as well as the growth of ovarian (2774) and cervical cancer cells (HeLa) [59].

Spinasterol has also been reported in *Cucurbita moschata*, *Conyza blinii*, *Gypsophila oldhamiana*, *Gordonia ceylanica*, and *Acacia cedilloi* [59-63]. The anticancer activity of spinasterol was demonstrated *in vivo* in studies that showed that it greatly decreased the incidence of skin tumors without co-carcinogen or co-tumor promoter activities [64].



61 R = H
62 R = Me
63 R = $(CH_2)_3$Me
64 R =

Figure 1: Steroid derivatives with acetylenic side chains as substrates of P-450scc which would generate a reactive species in the active site, thus leading to suicide inhibition of the enzyme.

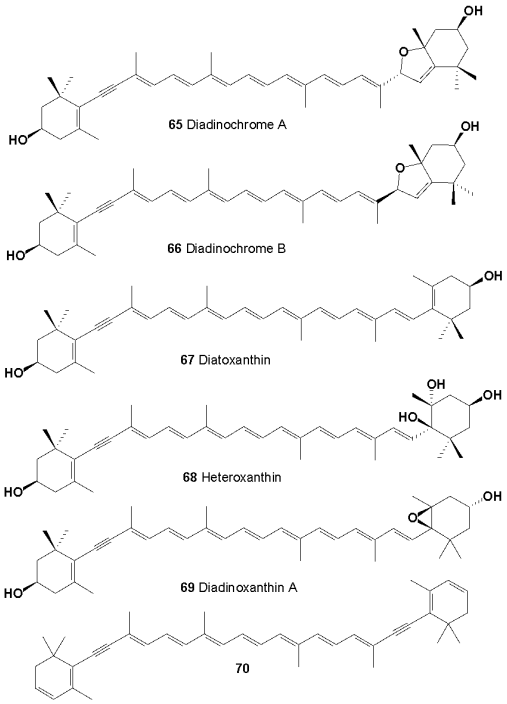
Several synthesized acetylenic steroids (**61-64**) having the same structure, except for the side chains, are excellent inhibitors of P-450scc, although they appear to inactivate the enzyme in a manner distinct from the action of acetylenes on the microsomal enzyme [65]. Incubation of (**69-72**) with P-450scc in the presence of electron donors and oxygen led to a time-dependent absorbance decrease in the Soret region. This absorbance decrease was found to be dependent on the presence of adrenodoxin, adrenodoxin reductase, NADPH, and oxygen. The proposed mechanism of P-450scc inhibition is shown in Figure 1. Additional activities for (**61**-**64**) steroids are found as prostaglandin-E2 9-reductase inhibitor.

Cytotoxic Carotenoids

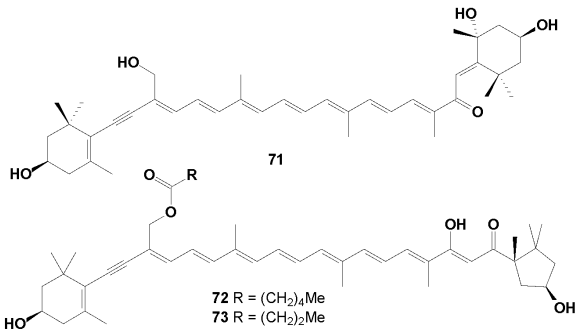
Three carotenoids with an acetylenic unit, named diadinochrome A (**65**) and B (**66**), and diatoxanthin (**67**) were isolated from the freshwater red tide organism *Peridinium bipes* (Dinophyceae) [66]. Diadinochrome A was shown to be cytotoxic to HeLa cells, while two other compounds exhibited anti-carcinogenic activity.

Extracts of *Peridinium bipes* exerted an inhibitory effect on the growth of *Microcystis aeruginosa* [67-69]. Tsushima and co-workers [68] studied 51 carotenoids, which including carotenoids with acetylenic unit(s): amarouciaxanthin B (sidnyaxanthin), crassostreaxanthin A, diatoxanthin, halocynthiaxanthin, heteroxanthin, mytiloxanthin, mytiloxanthinone, pectenol A and B, and pectenolone. Acetylenic carotenoids showed different cytotoxic activity against Raji cells (human neoplasm).

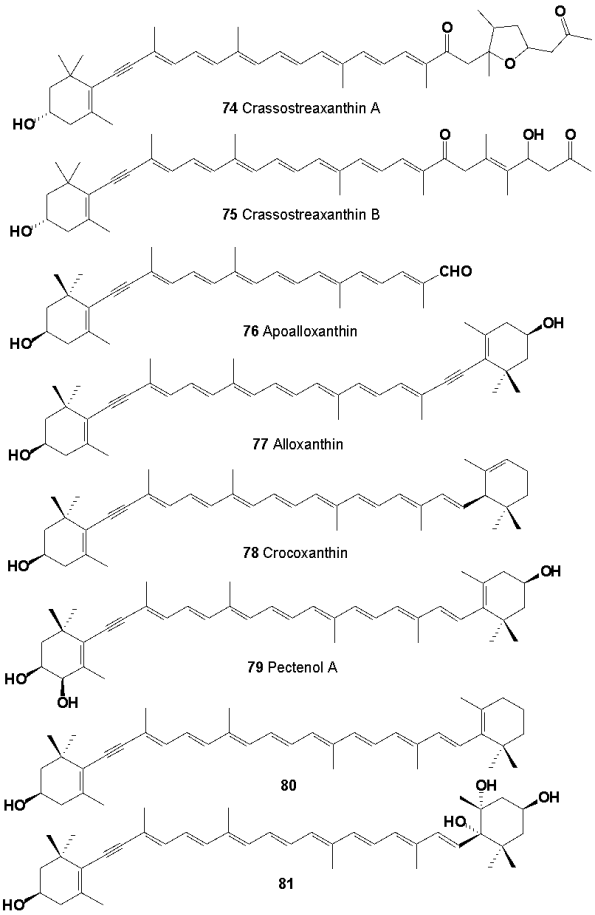
Quantitative carotenoid analysis of the microalga *Euglena viridis* revealed the presence of β,β-carotene (5% of total carotenoids), mixed with some β,ε-carotene, the β,ε-carotene derived siphonein (siphonaxanthin 19-dodecenoate, 8%), the allenic neoxanthin (4%), and acetylenic carotenoids > 86% [70-73].



Those included the mono-acetylenic diatoxanthin (**67**) (major, 61%), diadinoxanthin (**69**, rearranged to diadinochrome, 12%), heteroxanthin (**68**, 1%), and the diacetylenic 3,4,7,8,3',4',7',8'-octadehydro-β,β -carotene (**70**, 6%). The significance of the presence of siphonein and diacetylenic carotenoids for algal chemosystematics was briefly discussed.

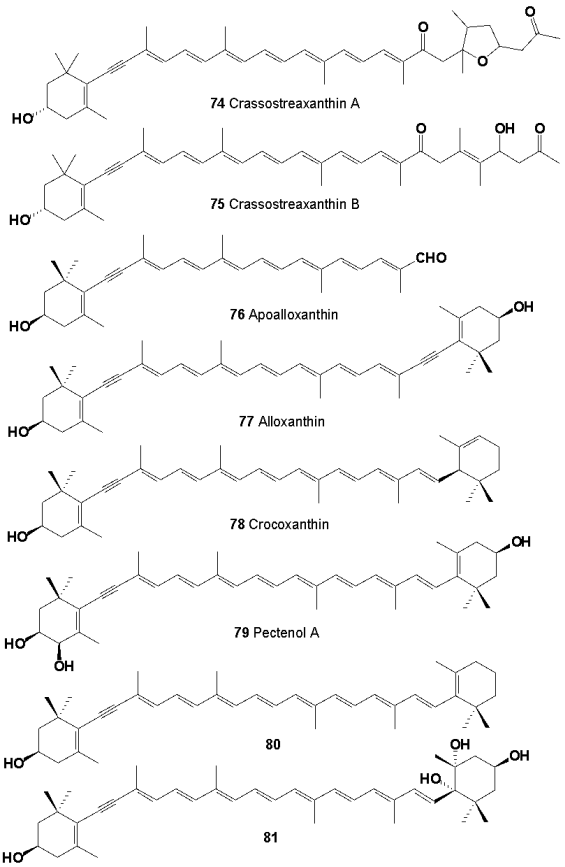


Heteroxanthin was also found in *Euglena gracilis*, and in some species of Xanthophyceae [71-73]. The principal crystallizable xanthophylls of *Tribonema aequale* were diatoxanthin, heteroxanthin, and diadinoxanthin [74]. Carotenoids of two members of the Raphidophyceae (chloromonads), *Gonyostomum semen* and *Vacuolaria virescens*, and of two tentative members of the same class (*Chattonella japonica* and *Fibrocapsa japonica)* were analyzed [75].



Group I (*G. semen* and *V. virescens*) showed a similar carotenoid pattern, comprised of diadinoxanthin (54-60% of total carotenoids), dinoxanthin (8-17%),β,β-carotene (7%), and heteroxanthin (7%), as well as neoxanthin (*G. semen*, 3%), an epoxidic monoacetate (*G. semen*, 12%), an epoxidic carotenol, possibly 9'-*cis*-diadinoxanthin (*V. virescens*, 8%), an epoxidic diacetate (*V. virescens*, 2%) and vaucheriaxanthin 3,19-diacetate (*V. virescens*, 8%). Characteristic features common to the carotenoids encountered are a high proportion of epoxidic carotenoids (78-86%), allenic carotenoids (24-82%), acetylated carotenols (18-81%), and acetylenic carotenoids (61-67%; Group I only). The xanthophycean cultured alga *Pleurochloris meiringensis* contains heteroxanthin, diadinoxanthin and β-carotene [76]. Carotenoids extracted from freshwater red tide plankton were shown to include β-carotene (8%), peridinin (26%), dinochrome A (14%), dinochrome B (3%), dino-

xanthin (2%), diadinochrome A (**65**, 3%), diatoxanthin (**67**, 7%), and 13'-*cis*-7',8'-dihydro-neoxanthin-20'-al 3'-β-lactoside (4.7%). The isolated carotenoids: β-carotene, dinochrome A, dinochrome B, dinoxanthin, diadinochrome A, diatoxanthin, and 13'-cis-7',8'-dihydroneoxanthin-20'-al 3'-β-lactoside have shown cytotoxic activities against some mouse tumor cell lines [77].

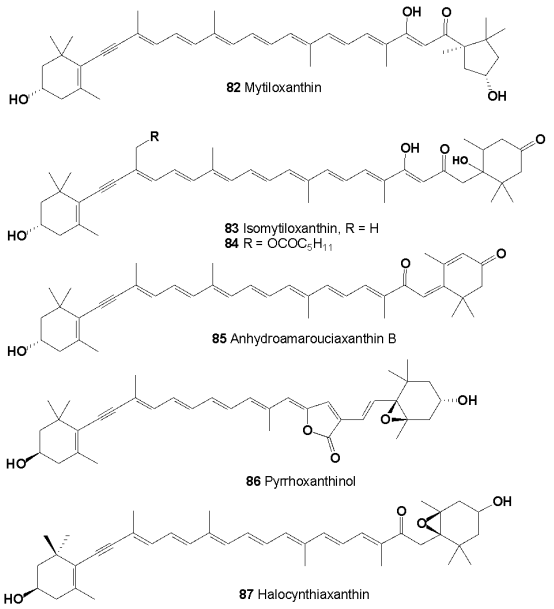


The marine sponge, *Prianos osiros* from Pohnpei, gave a new cytotoxic acetylenic carotenoid, 3,3',5,19'-tetrahydroxy-7',8'-didehydro-γ,ε-carotene-8-one (**71**), which was cytotoxic toward cultured human colon tumor cells, HCT 116 (IC_{50} 4.4 μg/mL) [78]. Two new carotenoids, the neoplasm inhibitors, 19-hexanoyl-oxymytiloxanthin (**72**) and 19-butanoyloxy-mytiloxanthin (**73**), have been isolated from the marine sponge *Phakellia stelliderma* collected in Okinawa. Both compounds showed mild cytotoxic activity against P388 mouse leukemia cells [79].

Cytotoxic carotenoids, named crassostreaxanthins A (**74**), and B (**75**), and apoalloxanthinal (**76**), were isolated from the oyster *Crassostrea gigas* (Ostreidae), and apocarotenoid was isolated (**80**) from the marine shellfish *Mytilus coruscus* [80,81].

Acetylenic carotenoids (**66, 68, 77, 78, 79**, 7,8-didehydro-β-cryptoxanthin **80**), and 6-epi-heteroxanthin have been isolated from three species of corbicula clams, *Corbicula japonica*, *C. sandai*, and *Corbicula* sp. (Chinese freshwater corbicula clam) [82].

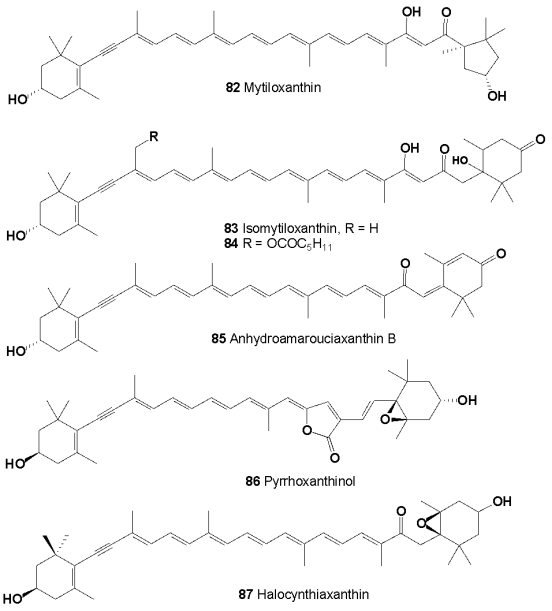
Total carotenoid content of the muscle of *Peronidia venulosa* and *Corbicula fluminea*, and of the gonad of *Atrina pinnata* and *Chlamys farreri* ranged from 2.5 to 6.8 mg per cent, values that are relatively higher than those of other shellfishes. The growth of HeLa cells by β-carotene, cynthiaxanthin, astaxanthin and halocynthiaxanthin, NCI-H87 cells by β-carotene, astaxanthin, cynthiaxanthin, and halocynthiaxanthin, HT-29 cells by β-carotene, cynthiaxanthin, mytilo- xanthin and halocynthia-xanthin, and MG-63 cells by β-carotene, cynthiaxanthin, astaxanthin, cantha-xanthin and halocynthiaxanthin were significantly reduced [83].



Several cytotoxic acetylenic carotenoids (**67, 68, 77, 79**), isomytiloxanthin (**83**), 19'-(hexanoyloxy)-isomytiloxanthin (**84**), hydroamarouciaxanthin B (**85**), pyrrhoxanthinol (**86**), and halocynthiaxanthin (**87**) have been identified from muscle of *Mytilus edulis* [84-88]. Diatoxanthin, alloxanthin, and pectinolone from *Pectene maximus* and *Patinopectene yessoensis*, pectinols A and B from *Mytilus coruscus*, crassostreaxanthins A and B from *Crassostrea gigas*, and a series of carotenoids with a 5,6-dihydro-β-end group from *Fushinus perplexus* have been reported as the principal carotenoids in marine shellfish [89-92]. Carotenoids in eight species of freshwater and sea mollusks from Russia were investigated [93]. Alloxanthin, mytiloxanthin, isomytiloxanthin, halocynthiaxanthin ether from *Modiolus modiolus*, and *Crenomytilus grayanus*; alloxanthin, and mytiloxanthin from *Mytilus galloprovincialis*; alloxanthin, mytiloxanthin, isomytiloxanthin, halocynthiaxanthin ether, and pectenolon from *Mizuhopecten yessoensis* have been isolated [93,94].

From the calyx and arms of *Lamprometra klunzingeri* (family Mariametridae, class Crinoidea, Echinodermata), collected in the Red Sea, the cytotoxic carotenoids diadinochrome (**65**), al-

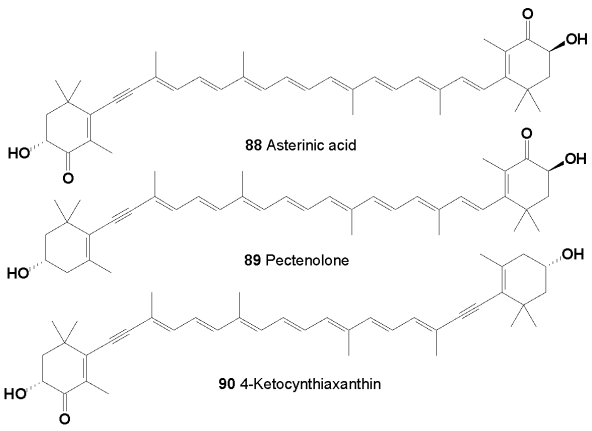
loxanthin (**77**), cynthiaxanthin, pectenoxanthin, and asterinic acid (**88**) have been isolated [95].



Asterinic acid (**88**) was found in Echinoderms from the Adriatic Sea: *Coscinasterias tenuispina, Marthasterias glacialis, Paracentrotus lividus,* and *Sphaerechinus granularis* [96]. The cytotoxic acetylenic carotenoids diatoxanthin, and alloxanthin were present in the gonads of Australian and Japanese species of the echinoids *Heliocidaris erythrogramma* and *H. tuberculata*; in the sea urchin *Pseudocentrotus depressus*; in *Peronella japonica*; in seven species of sea-urchins, belonging to the orders Cidaroida, Echinothurioida, Diadematoida, and Arbacioida, as well as pectenolone (**89**) and 4-keto-cynthiaxanthin (**90**) [97-100].

Asterinic acid was isolated from *Asterias rubens*, *Acanthaster planci*, *Coscinastrias acutispina*, *Leiaster leachii*, *Asterias amurensis*, *Ophidiaster ophidianus*, *Asterina panceri*, *Asteropecten aurantiacus*, and *Marthasterias glacialis* [101-106]. Mytiloxanthin was found in *Ophiocomina nigra*; and derivatives of the cytotoxic acetylenic carotenoids, (3S,4S,3'S,5'R)-4-hydroxy-mytiloxanthin, (3S,4S,3'S,4'S)-4,4'-dihydroxy-diatoxanthin, (3S,4S,3'S,4'S)-4,4'-dihydroxyalloxanthin, (3S,3'S,4'S)-4-keto-4'-hydroxydiatoxanthin, and (3S,3'S,4'S)-4-keto-4'-hydroxy-alloxanthine were isolated from the starfish species *Asterina pectinifera* and *Asterias amurensis* [107,108].

The carotenoid content of the seven species of sea cucumber (*Stichopus japonicus*, *Holothuria leucospilota*, *H. moebi*, and *H. pervicax* of the order Aspidochirotida, *Cucumaria japonica*, *C. echinata*, and *Pentacta australis* of the order Dendrochirotida) was reported [109]. β-Carotene, β-echinenone, canthixanthin, phoenicoxanthin, and astaxanthin were common in all the sea cucumbers examined. Alloxanthin, diatoxanthin, and pectenolone were isolated as minor carotenoids. The bluish violet pigment in the dorsal skin of *Asterias rubens* was isolated as an amorphous powder [110].



Asterinic acid (**100**) and four derivatives of alloxanthin, diatoxanthin, and mytiloxanthin were isolated and their structures elucidated. More detailed information on the carotenoids and other bioactive compounds was also reported [111-113].

CONCLUSION

Intensive searches for new classes of pharmacologically potent agents produced by bacteria, cyanobacteria, micro- and macroalgae, marine and freshwater invertebrates, plants, and fungi have resulted in the discovery of dozens of compounds possessing high cytotoxic activities. However, only a limited number of them have been tested in pre-clinical and clinical trials. One of the reasons is a limited supply of the active ingredients from natural sources. However, the pre-clinical and clinical development of many terrestrial and aquatic derived natural products into pharmaceuticals is often hampered by a limited supply from the natural source.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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