

## Sphingolipids from Marine Organisms: A Review<sup>§</sup>

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**Abstract** – The sphingolipids isolated from marine organisms and their biological activities have been reviewed.

**Key words** – Marine organisms, sphingolipids, biological activity.

### Introduction

The history of an extremely interesting group of natural products called sphingolipids or ceramides was initially born out of studies on the chemical constitution of the brain cells as early as 1880 (Thudichum, 1884). The compounds attracted the attention of chemists and biochemists by their involvement in diverse cellular processes including cell growth, survival, differentiation, and adhesion (Springer and Lasky, 1991; Fiezi, 1991).

The sphingolipid [1] may be, for convenience, considered to be composed of three principal structural moieties: (i) the sphingoid base [2] (ii) the polar functionality, and (iii) carboxy alkyl function. The most commonly occurring sphingoid bases from animal and plant sources are sphingosine [3] and phytosphingosine [4], respectively. The first sphingosine preparation was obtained in 1880 by Thudichum and the correct structure was proposed later (Carter *et al.*, 1942; 1947). Variations in chain length, presence or absence of double bonds and hydroxyls, including the position and stereochemistry, glycosidation and phosphorylation produce a large structural diversity in sphingolipids. The efforts of chemists around the world had led to the isolation of large number of sphingolipids from animal as well as plant sources on the land, in fresh water, and marine systems. There are more than 300 sphingolipids that have been identified to occur in nature (Wang *et al.*, 2000). In addition to the natural sources, a good number of compounds were synthesized in the laboratories by chemists inspired by the interesting bioactivities and necessity of the compounds in sufficient quantities for

further investigations.

This review is intended to incorporate the sphingolipids, isolated and characterized from marine sources until 2002. After the first recognition of sphingolipids in 1970 (Vaskovskii *et al.*, 1970), a large number of sphingolipids have been isolated from various marine organisms including algae, sponges, sea anemones, sea stars, tunicates, soft corals etc. Some sphingolipids exhibited antitumor, immunostimulatory, antimicrobial, antiviral, Ca<sup>2+</sup>-ATPase activation or phospholipase A2 inhibition activity. An  $\alpha$ -galactosyl ceramide (KRN 7000), a derivative of agelasphins isolated from the sponge *Agelas mauritianus*, is under phase I clinical trials as anticancer compound (Kikuchi *et al.*, 2001) and also reported to reduce pancreatic inflammation and diabetes (Naumov *et al.*, 2001). Biological activities of the sphingolipids from marine organisms are summarized in Table 1 (Faulkner, 2002; John *et al.*, 2003).

**Algae** – A mixture of five caulerpicins [5] was isolated from Sri Lankan green algae *Caulerpa racemosa* (Mahendran *et al.*, 1979). A new ceramide, sertularamide [6], was isolated from the green algae *Caulerpa sertularioides* (Xu *et al.*, 1997). A mixture of ceramides derived from 2-amino-4E-alkene-1, 3-diol sphingenines with C22, C23, and C24 saturated fatty acid residues was isolated from the red alga *Ceratodictyon spongiosum* Zanardini (Rhodymeniaceae) containing the symbiotic sponge *Sigmadocia symbiotica* (Lo *et al.*, 2001). Coralipid [7] is a galactosyl sphingolipid obtained from the Japanese red algae *Corallina pilulifera* (Ishida *et al.*, 1993). Chemical examination of the red alga *Halymenia durivilliae*, collected on the coast off Andaman and Nicobar Islands yielded a new sphingosine derivative [8] (Bheemasankararao and Satyanarayana, 1994). Halymimine [9], an unusual ceramide, was isolated from *Halymenia porphyroides* (Bano *et al.*, 1990). An antiviral sphingosine derivative [10] was isolated from the green alga *Ulva fasciata* collected along the West coast of the Indian Peninsula (Garg

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<sup>§</sup>Dedicated to D.J. Faul Kner

**Table 1.** Biological activities of sphingolipids from marine organisms

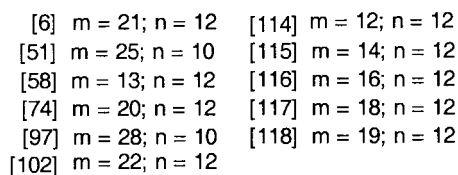
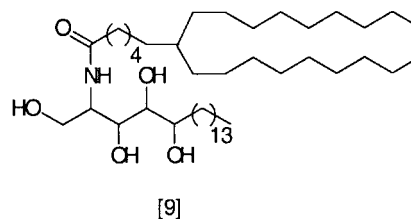
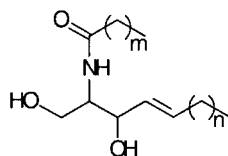
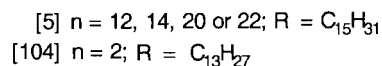
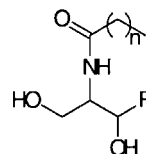
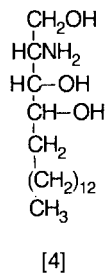
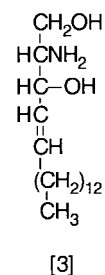
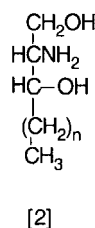
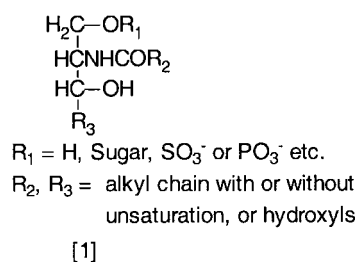
Organism	Activity	Compound No.	Reference
<i>Ulva fasciata</i>	Antiviral	10, 11	Garg <i>et al.</i> , 1992; Sharma <i>et al.</i> , 1996
<i>Flavobacterium</i> sp.	DNA polymerase $\alpha$ inhibition	14, 15	Kobayashi <i>et al.</i> , 1995
<i>Symbiodinium</i> sp.	Sarcoplasmic reticulum $Ca^{2+}$ -ATPase activator	17	Kobayashi <i>et al.</i> , 1998
<i>Agelas</i> sp.	Cancer cell growth inhibitor	22	Pettit <i>et al.</i> , 1999
<i>A. dispar</i> , <i>A. conifera</i>	Immunostimulating activity	25, 28-31	Costantino <i>et al.</i> , 1996
<i>A. mauritanus</i>	Antitumor and immunostimulatory	34-40	Natori <i>et al.</i> , 1993; 1994; Akimoto <i>et al.</i> , 1993
<i>Chondropsis</i> sp.	Histidine decarboxylase inhibition	53	Endo <i>et al.</i> , 1986; Honda <i>et al.</i> , 1991
<i>Discodermia calyx</i>	Neuraminidase inhibition	54-56	Nakao <i>et al.</i> , 2001
<i>Halichondria cylindrata</i>	Antifungal and Cytotoxic	60-69	Li <i>et al.</i> , 1995
<i>Haliclona koremella</i>	Antifouling	75	Hattori <i>et al.</i> , 1998
<i>Iotrochota ridley</i>	Cytotoxic	82	Deng <i>et al.</i> , 2001
<i>Plakortis simplex</i>	Immunosuppressive	93, 94	Costantino <i>et al.</i> , 1997
<i>Calicogorgia</i>	Lethal against muriid gastropod	115-117	Ochi <i>et al.</i> , 1992
<i>Watersipora cucullata</i>	DNA Topoisomerase I inhibition	126, 127	Ojika <i>et al.</i> , 1997
<i>Cystodytes cf. dellechiaiei</i>	Phospholipase A2 inhibition	128	Loukaci <i>et al.</i> , 2000
<i>Asterias amurensis versicolor</i>	Neuroblastoma cell growth inhibition	164	Higuchi <i>et al.</i> , 1993
<i>Astropecten latespinosus</i>	Antitumor	168	Higuchi <i>et al.</i> , 1995
<i>Luidia maculata</i>	Neuritogenic	173,174	Kawatake <i>et al.</i> , 1997; 1999
<i>Ophidiaster ophidiamus</i>	Cytotoxic	175-178, 38	Jin <i>et al.</i> , 1994
<i>Pentaceraster regulus</i>	Wound-healing	179	Venkannababu <i>et al.</i> , 1997
<i>Cucumaria echinata</i>	Brine shrimp toxicity and neuritogenic	190-194	Yamada <i>et al.</i> , 1998a
<i>Holothuria leucospilota</i>	Neuritogenic	196-197	Yamada <i>et al.</i> , 2001
<i>Holothuria pervicax</i>	Neuritogenic	199-200	Yamada <i>et al.</i> , 1998b; 2000
<i>Stichopus japonicus</i>	Neuritogenic	206	Kaneko <i>et al.</i> , 1999

*et al.*, 1992). Another sphingosine derivative [11] was also reported from the same species from India as antiviral constituent (Sharma *et al.*, 1996).

**Microorganisms and Phytoplankton** – A new ceramide [12] bearing a 2-hydroxy-15-methyl-3-octadecenoyl moiety was isolated from the epiphytic dinoflagellate *Coolia monotis* (Tanaka *et al.*, 1998). This is the first report of a  $C_{18}$  fatty acid with a methyl group substituted at C-15 carbon from natural sources. A sulfonic acid analogue of ceramide [13] was isolated from the gram-negative marine bacterium *Cyclobacterium marinus* (Batrakov *et al.*, 1998). Two sulfonolipids, flavocristamides A [14] and B [15] which inhibit calf thymus DNA polymerase  $\alpha$  were isolated from a marine bacterium *Flavobacterium* sp. (Kobayashi *et al.*, 1995). The marine fungus *Lignicola laevis* on large scale culturing yielded a ceramide (Abraham *et al.*, 1994). A novel sphingosine glycoside having (3'E, 4E)-1,3-dihydroxy-2-[(2'-hydroxy octadecanoyloxy) amino]-10-methyl-3',4,9-octadecatriene as ceramide was obtained from the marine fungus *Fusarium* sp. (#2489) from the South China Sea (Li *et al.*, 2002). A marine fungus, *Microsphaeropsis olivacea*, isolated from an unidentified Florida sponge, produced a cerebroside [16] (Keusgen *et al.*, 1996). A novel sphingosine derivative, symbioramide [17], has been isolated from the laboratory-cultured marine dinoflagellate *Symbiodinium* sp. as a sarcoplasmic reticulum  $Ca^{2+}$ -ATPase activator (Kobayashi *et al.*, 1988). Symbioramide-C16 [18], a new ceramide was

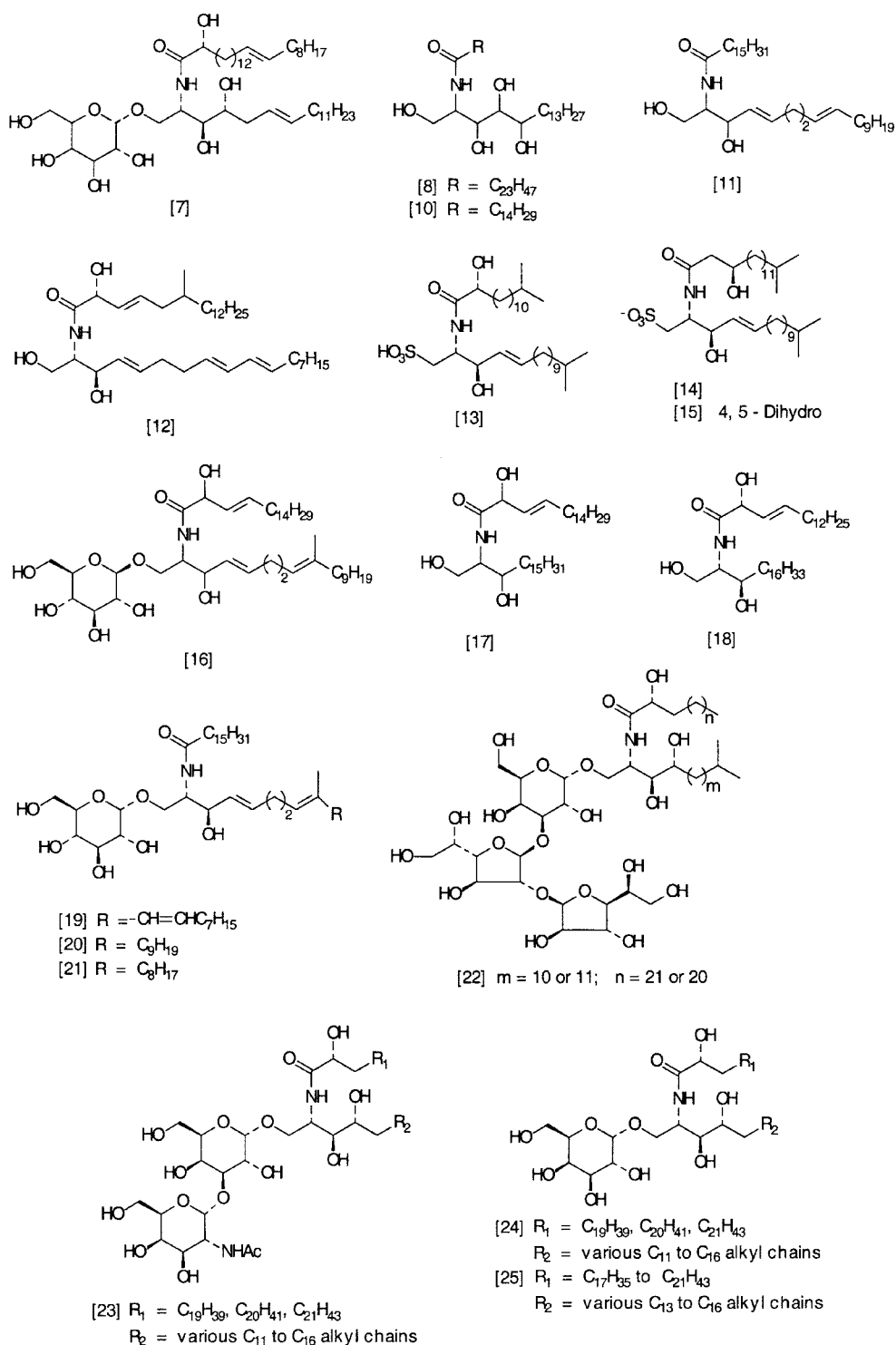
isolated from the same species (Nakamura *et al.*, 1998). Three new glycosphingolipids, thraustochytriosides A-C [19-21] were produced, by a cultured marine protist *Thraustochytrium globosum* collected in the Bahamas (Jenkins *et al.*, 1999).

**Sponges** – A human cell line bioassay-directed investigation of the sponge *Agelas* sp. from Papua New Guinea led to the isolation of a new cerebroside agelagalastatin [22] which inhibited the growth of the cancer cell. It is the first report of a natural product containing a digalactofuranosyl unit (Pettit *et al.*, 1999). Four unusual  $\alpha$ -glycosylceramides [23-27] were isolated, each as a mixture of homologs, from the Caribbean sponge *Agelas clathrodes* (Costantino *et al.*, 1995a). Some more glycosphingolipids [25, 28-30] of the same type, in addition to those previously reported, were isolated from *A. conifera* and *A. longissima* (Cafieri *et al.*, 1995; Costantino *et al.*, 1995b). In addition to the above, a novel triglycosyl ceramide [31] was isolated as a major component of the mixture obtained from the *A. dispar* collected along the Coast of San Salvador Island (Bahamas). All the compounds were tested for immunostimulating activity using the mixed lymphocyte reaction (MLR) assay along with other glycosyl ceramides from *A. conifera* and structure-activity relationship was established. The compounds having a free 2-OH on the sugar directly linked to the ceramide moiety exhibit immunostimulating activity (Costantino *et al.*, 1996). Longiside [32], a digalactosyl



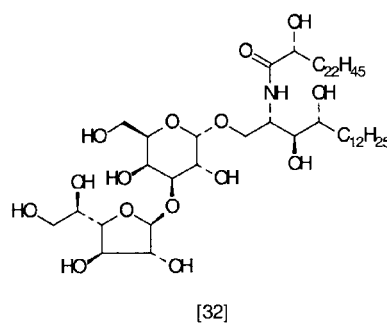
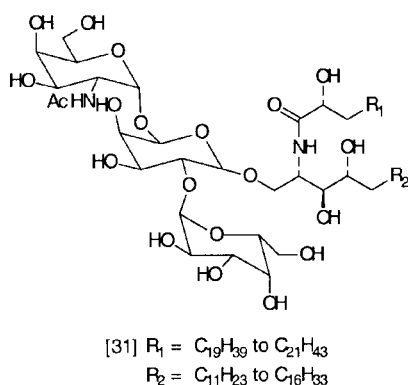
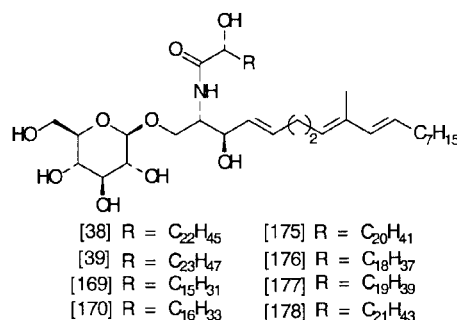
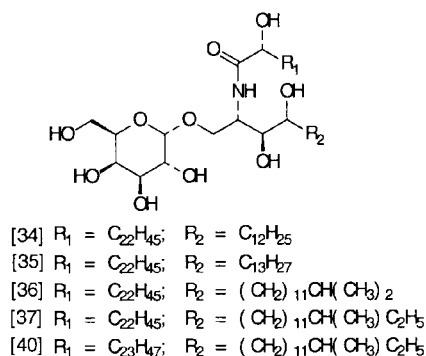
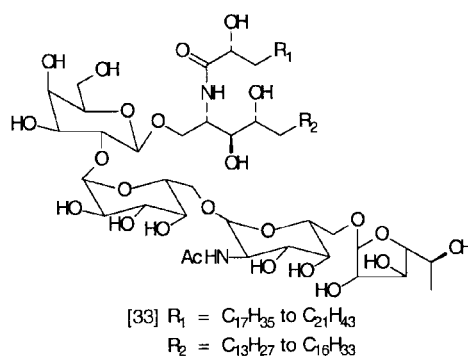
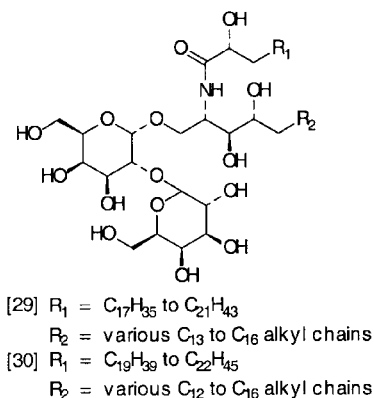
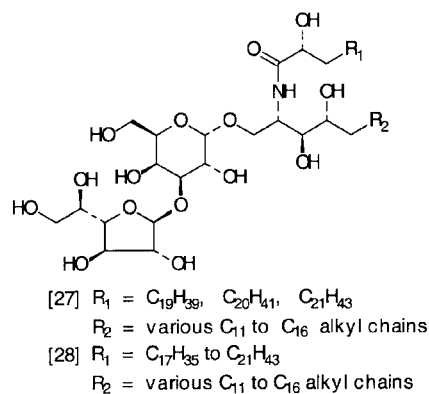
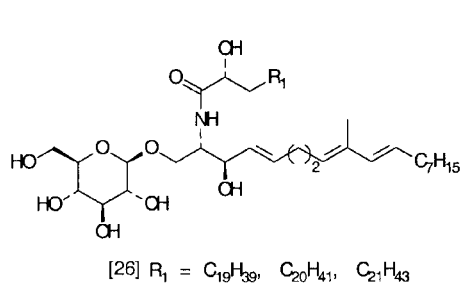
ceramide with one galactose in the unusual  $\beta$ -furanose form (Cafieri *et al.*, 1994), a tetraglycosylated sphingolipid [33] were isolated from the Bahamas sponge *A. longissima* (Cafieri *et al.*, 1996). Antitumor and immunostimulatory glycosphingolipids, agelasphins-7a, -9a, -9b, -10, 11, 12, and 13 [34-40] possessing an  $\alpha$ -galactose unit were isolated from the Okinawan sponge *A. mauritanus*. The absolute stereochemistry of agelasphin-9b was determined by total synthesis. All agelasphins showed antitumor activity (Natori *et al.*, 1993; 1994; Akimoto *et al.*, 1993). One agelasphin analogue KRN 7000 showed interesting anticancer activity and it is now under phase I clinical trials as anticancer agent (Kikuchi *et al.*, 2001). The compound is also reported to reduce pancreatic inflammation and diabetes (Naumov *et al.*, 2001). Amphicerebrosides B-F [41-45] were isolated from the sponge *Amphimedon viridis* collected in the Red Sea (Hirsch and Kashman, 1989). Three glycosphingolipids [46-48] were obtained from *Aplysinella rhax* collected in New Caledonia (Borbone *et al.*, 2001). Two new glycosphingolipids, axiceramides A [49] and B [50], were isolated as their peracetates from a La Reunion species of *Axinella* (Costantino *et al.*, 1994). A new ceramide,

biemnamide [51], was obtained from the marine sponge *Biemna* sp. collected from the South China Sea and its structure was established by spectroscopic data (Zheng *et al.*, 1995). Chemical investigation of the sponge *Callyspongia spinosissima* furnished a ceramide [52] (Agarwal and Garg, 1997). A cerebroside mixture was isolated and characterized from the marine sponge *Chondrilla nucula* (Schmitz and McDonald, 1974). A cerebroside [53] which showed histidine decarboxylase inhibition activity was isolated from a *Chondropsis* sp. (Endo *et al.*, 1986; Honda *et al.*, 1991). New ceramide homologues, possessing iso- and anteiso-long chain, were isolated from the marine sponge *Clathria fasciculata* from the South China Sea near Hainan Island, China. The fatty acid part was mainly composed of (4E)-2-hydroxy-4-docosenic, tricosenic, tetracosenic, and pentacosenic acids (Xiao *et al.*, 2002). Three sulfated ceramides, calyceramides A-C [54-56] with neuraminidase inhibition activity were obtained from a Japanese collection of *Discodermia calyx* (Nakao *et al.*, 2001). Chemical examination of the sponge *Dysidea etheria* furnished ceramides (Grode, 1983). An acetylated tetrahydroxy ceramide [57] was isolated from an acetylated extract of *Fascispongia cavernosa* collected



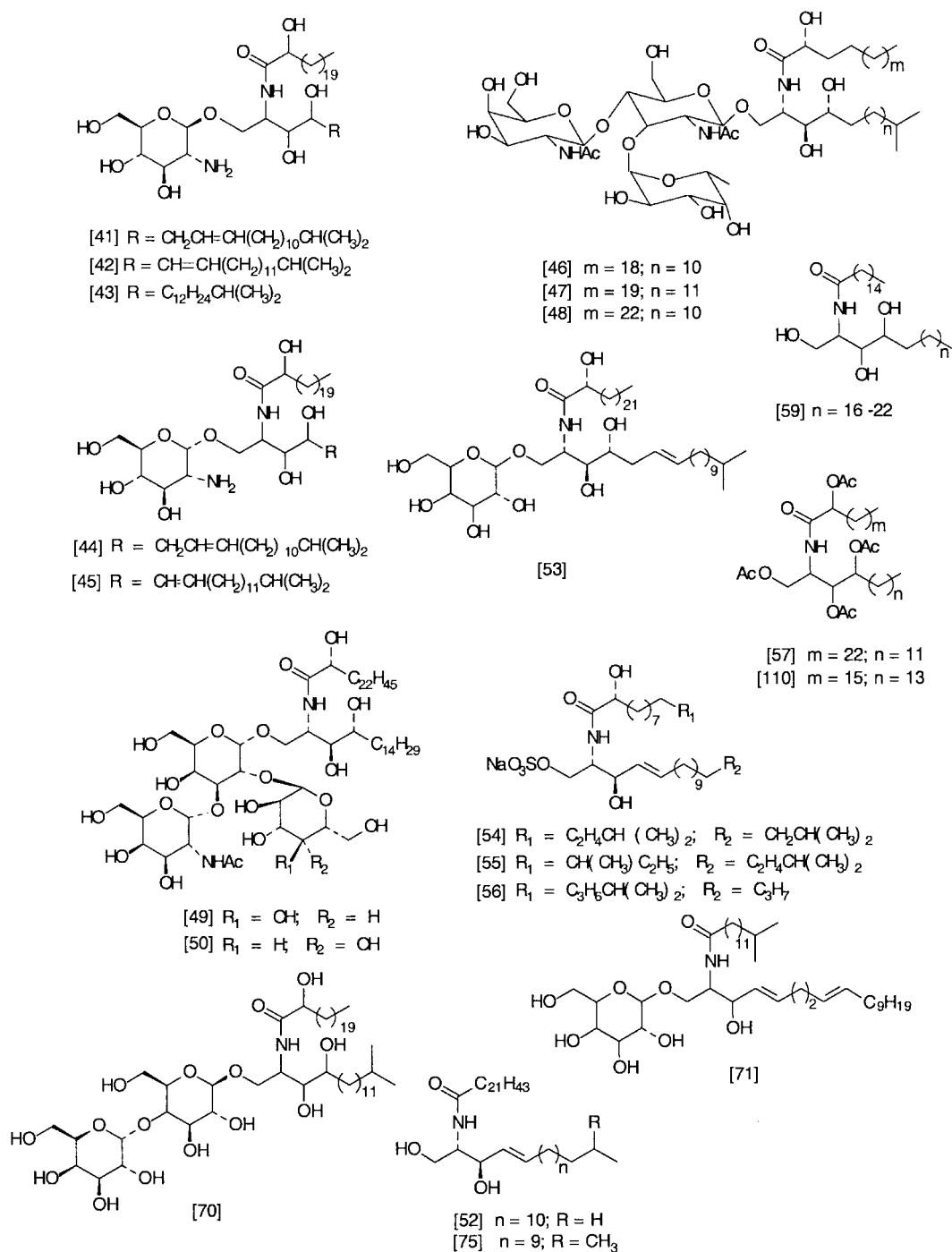
on the South East Coast of India (Ramesh *et al.*, 2001). A sphingosine derivative [58] was obtained from the South China Sea sponge *Gallius cymiformis* (Xiao *et al.*, 1999). The marine sponge *Grayella cyatophora* furnished several new homologous sphingosines [59] having the same acyl substituent (Michele and Michele, 2002). Ten glycosphingolipids,

halicylindrosides A<sub>1</sub>-A<sub>4</sub> [60-63], and B<sub>1</sub>-B<sub>6</sub> [64-69] having  $\beta$ -*N*-acetylglucosamine as sugar unit were isolated from a Japanese sponge *Halichondria cylindrata*. These compounds were moderately antifungal against *Mortierella remaniana* and cytotoxic against P388 murine leukemia cells (Li *et al.*, 1995). A ceramide digalactoside [70] was obtained as



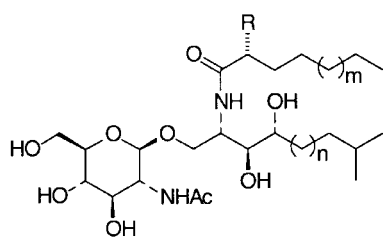
major glycosphingolipid from the sponge *Haliclona japonica* (Hayashi *et al.*, 1991). A novel glycosphingolipid [71] containing an iso-fatty acid was isolated for the first time along with a galactosyl ceramide [72] from the Oregon marine sponge *Haliclona panicea* (Nagle *et al.*, 1992). Halicerebroside A [73] was obtained from the sponge of the

genus *Haliclona* (Hirsch and Kashman, 1989). A species of the genus *Haliclona* from the Gujarat coast in India furnished a known ceramide [74] (Parameswaran *et al.*, 1994). A ceramide [75] that inhibits fouling by macroalgae was isolated from *Haliclona koremella* collected in Palau (Hattori *et al.*, 1998). The separate chemical examination

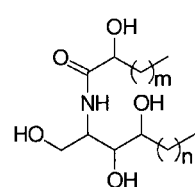
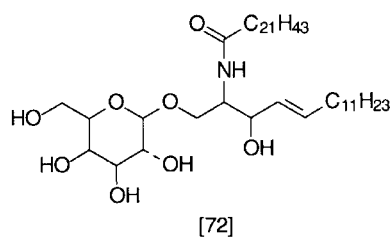


of the sponges *Halichondria tenuiramosa*, *Tedania anhelens*, *Zygomycale parishii*, and *Sigmadocia pumila* collected from the Mandapam coast of Indian Ocean yielded four ceramides [76-79], respectively, each as a mixture of homologues. These are unique for branching on both the sphingosine base and fatty acid chain (Venkateswarlu *et al.*, 1998). A mixture of cerebroside was reported from a Far-Eastern sponge *Hymeniacidon assimilis* (Makareva *et al.*, 1989).

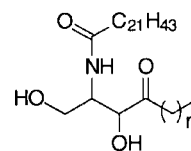
Two new ceramides [80, 81] and a cytotoxic glycosphingolipid [82] were isolated from the Chinese marine sponge *Iotrochota ridley* collected from South China Sea. The fatty acyl part of the glycosphingolipid has a *cis* double bond which is uncommon in natural sphingolipids (Liyan *et al.*, 2000; Deng *et al.*, 2001). Chemical investigation of the marine sponge *Ircinia variabilis* collected in the Bay of Naples yielded three new ceramides, variceramides [83-85]. These differed from natural ceramides only in the sphinganine



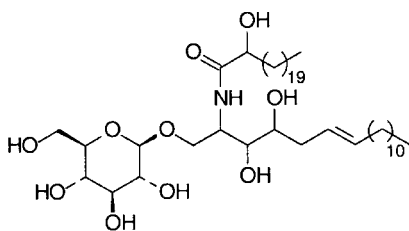
- [60]  $m = 16; n = 10; R = H$   
 [61]  $m = 16; n = 11; R = H$   
 [62]  $m = 17; n = 11; R = H$   
 [63]  $m = 18; n = 11; R = H$   
 [64]  $m = 16; n = 8; R = OH$   
 [65]  $m = 17; n = 8; R = OH$   
 [66]  $m = 16; n = 9; R = OH$   
 [67]  $m = 16; n = 10; R = OH$   
 [68]  $m = 17; n = 9; R = OH$   
 [69]  $m = 16; n = 11; R = OH$



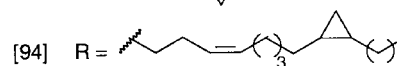
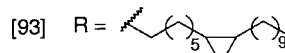
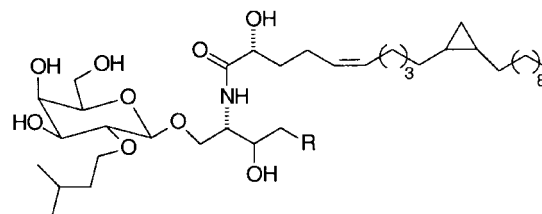
- [80]  $m = 21; n = 13$   
 [109]  $m = 11; n = 18$



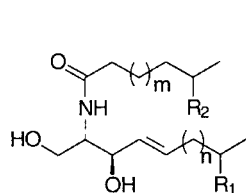
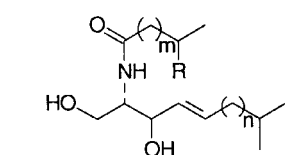
- [83]  $n = 12$   
 [84]  $n = 13$   
 [85]  $n = 14$



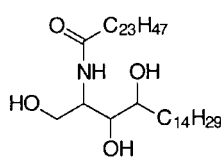
[73]



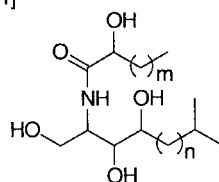
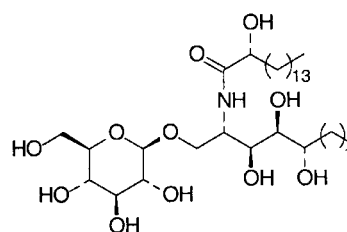
- [76]  $R = Me; m = 16, 17, 18, 19; n = 9, 10, 11$   
 [77]  $R = H; m = 18, 19, 20, 21, 22, 23; n = 9, 10, 11$   
 [78]  $R = H; m = 20, 21, 22, 23; n = 10$   
 [79]  $R = H; m = 19, 20, 21, 22, 23; n = 10, 11$



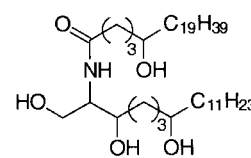
- [86]  $n = 9; m = 17; R_1 = H; R_2 = Me$   
 [87]  $n = 9; m = 17; R_1 = R_2 = Me$   
 [88]  $n = 9; m = 18; R_1 = Me; R_2 = H$   
 [89]  $n = 10; m = 17; R_1 = R_2 = Me$   
 [90]  $n = 10; m = 17; R_1 = Et; R_2 = H$   
 [91]  $n = 10; m = 17; R_1 = Et; R_2 = Me$



[81]

[96]  $m = 20, 21, 22; n = 10, 11, 12$ 

[92]



[95]

moieties, which possess a carbonyl function at position 4 in addition to amide carbonyl in the molecule (Cafieri and Fattorusso, 1990). A series of ceramides, oceapins A-F [86-91], which are unique for branching at both the sphingosine and fatty acid chains, were isolated as pure compounds

from the haplosclerid sponge *Oceanapia cf. tenuis* of Coral Sea. The absolute configuration was secured via protection of C (1')-OH and Mosher's esterification at C(3')-OH of the oceapins (Mancini *et al.*, 1994). A sponge *Phacellia fusca* Schmidt, collected from the Xisha Islands in the South China

Sea, yielded a novel cerebroside, Phaceliacerebroside A [92] (Xu *et al.*, 2001). A sponge of the genus *Phyllospongia* yielded a ceramide, phylloamide A (Wan *et al.*, 1997). Two unique glycosphingolipids belonging to a new class of prenylated glycolipids, Plakoside A [93] and B [94], have been isolated from the marine sponge *Plakortis simplex*. These plakosides are strongly immunosuppressive on activated T cells and proved to be useful natural model for an improved comprehension of the structural requirements for immunomodulating activity of glycosphingolipids (Costantino *et al.*, 1997). A novel ceramide [95] was isolated from South China Sea sponge *Polymastia sobustia*. This ceramide possess hydroxy groups on 5' and 7-positions of the fatty acid and sphingosine base, respectively (Xu and Zeng, 2001). A mixture of homologs, ptiloceramides, [96] was isolated from the sponge *Ptilocaulis spiculifer* (Hirsch and Kashman, 1989). A new ceramide, cymiforamide, N-triacontanoyl-hexadecaphingosine, [97] was isolated from the sponge *Sigmadocia cymiformis* Espar (Wang *et al.*, 2002). A novel sphingolipid [98] was reported from the sponge *Spirastrella inconstans* collected from the Eastern Coast of India. This is the first report of a sphingolipid isolated from a marine source in which the double bond has migrated to the C-6 position, allylic to the 4 hydroxyl group (Garg and Agarwal, 1995). A ceramide, N-docosamido sphingosine, was isolated from the sponge *Stelletta tenuis* (Meng *et al.*, 1996).

**Soft corals** – A new glycosphingolipid [99] with a branched sphingosine base was isolated from the soft coral *Cladiella* sp. collected from Andaman Islands (Dmitrenok *et al.*, 2001). Humesamide [100] is a ceramide obtained from the soft coral *Cladiella humesi* from Hainan, China (Yang *et al.*, 2000). A sphingosine derivative was isolated from the soft coral *Heteroxenia gardaquiensis* collected at the entrance of the Gulf of Suez (Hirsch and Kashman, 1989). A mixture of sphingosines which contains N-palmitoyl-2-amino-1,3-dihydroxy octadeca-4,8-diene [101] as major constituent was reported from two soft corals- a new species of *Lobophytum* and *Sinularia conferta* collected from Andaman and Nicobar Islands (Subrahmanyam *et al.*, 1996). Lobophytamide-L<sub>5</sub> [102] and lobophytamide-L<sub>8</sub> [103] were new ceramide compounds isolated from Chinese soft coral *Lobophytum chevalieri* (Li *et al.*, 1989). A new ceramide [104] was isolated from the Indian Ocean soft coral *Lobophytum crassum* (Vanisree and Subbaraju, 2002). The soft coral *Lobophytum microspiculatum* collected from Nansha Island, China, yielded microspicamide [105] (Xu *et al.*, 1998). A new sphingosine derivative [106] was isolated from the soft coral *Sinularia* sp. of the Andaman and Nicobar Islands (Anjaneyulu and Radhika, 1998). Two ceramides, sinumeramide and N-acetyl dihydrosphingosine,

were obtained from three species of Chinese soft corals of the genus *Sinularia* (Su *et al.*, 1989). Chemical examination of the soft coral *Sinularia crassa* of Andaman and Nicobar Islands yielded two sphingosine derivatives [101, 107] (Anjaneyulu and Radhika, 1999). A sphingolipid [108] was isolated from *Sinularia gravis* collected from South India (Anjaneyulu *et al.*, 1999) while *Sinularia leptoclados* collected from Andaman and Nicobar Islands yielded two sphingolipids [109, 110] (Reddy *et al.*, 1999).

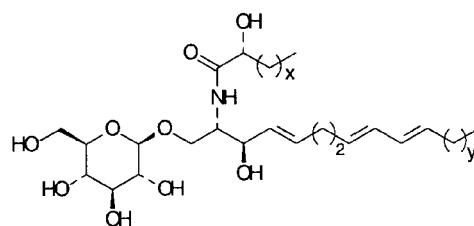
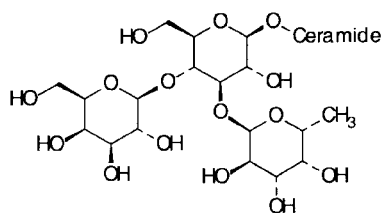
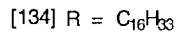
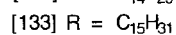
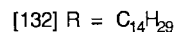
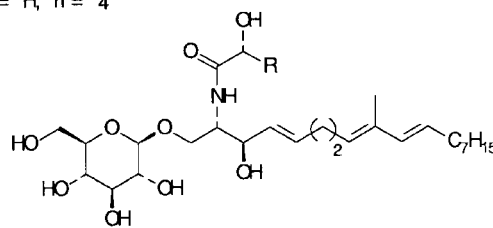
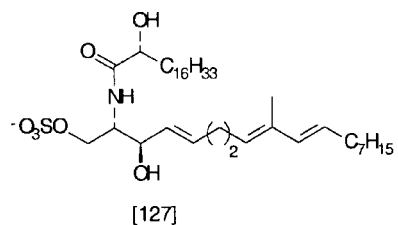
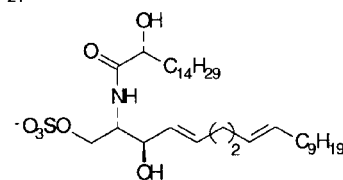
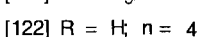
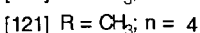
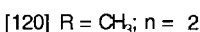
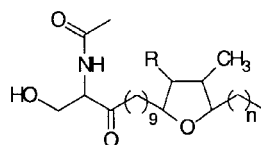
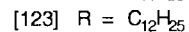
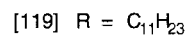
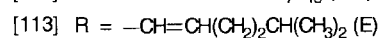
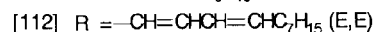
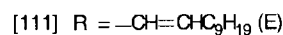
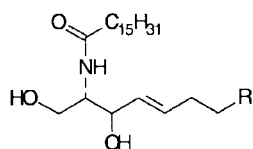
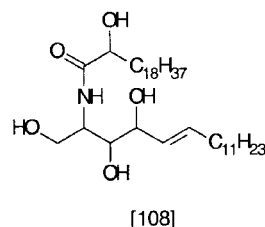
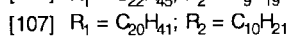
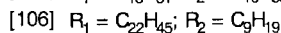
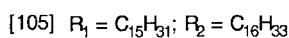
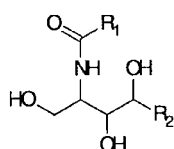
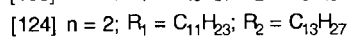
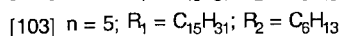
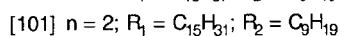
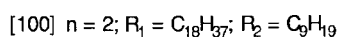
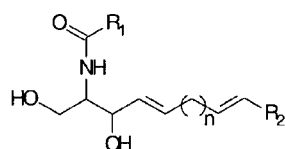
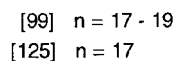
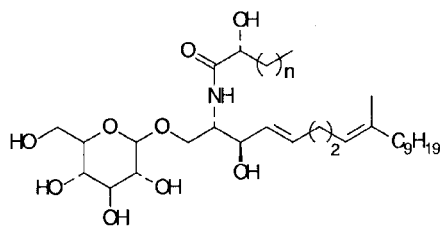
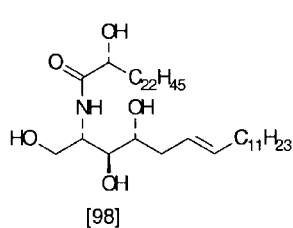
**Gorgonians** – Three new ceramides [111-113] along with a known ceramide [114] were isolated from bright red gorgonian *Acabaria undulata* collected along the shore of Keomun Island, Korea (Shin and Seo, 1995). Three novel bioactive sphingosine derivatives, calicogorgins A, B, and C [115-117] were isolated from the gorgonian *Calicogorgia* sp. and structures were determined by spectral and chemical methods. All these calicogorgins showed lethality against murine gastropod *Drupella fragum* (Ochi *et al.*, 1992). A novel ceramide, isisamide, was isolated from South China Sea gorgonian of the genus *Isis* (Deng *et al.*, 1994). The gorgonian *Isis minorbranchlata* collected from South China Sea furnished a ceramide (Yang and Su, 1994). Six N-acyl sphingosines [118-122, 74] were isolated from the Chinese gorgonian *Junceella squamata* (Li, 1995). Chemical examination of gorgonian *Pseudopterogorgia* sp. of the Indian Ocean yielded a ceramide [123] (Vanisree *et al.*, 2001).

**Sea Anemones** – Chemical examination of the sea anemone *Actinogeton* sp. from Japan yielded a new cerebroside (Sugita *et al.*, 1994). A new sphingosine derivative [124] was isolated from the tentacles of the *Anemonia sulcata* collected near Sousse, Tunisia (Chebaane and Guyot, 1986). A ceramide, 4E, 8E-sphingol-n-hexadecamide, causing morphological deformation to *Pyricularia oryzae* mycelia, was isolated by bioassay-guided fractionation from the sea anemone *Anthopleura pacific* (Zhang *et al.*, 2002). A sea anemone *Metridium senile* yielded a cerebroside [125] (Karlsson *et al.*, 1979). A ceramide [111] was obtained from the hypotensive extract of the sea anemone *Paracondylactis indicus* (Chakrabarty *et al.*, 1994).

**Bryozoans** – Two novel ceramide-1-sulfates [126, 127] were isolated as new potent human DNA topoisomerase I inhibitors from the Japanese Bryozoa *Watersipora cucullata* (Ojika *et al.*, 1997).

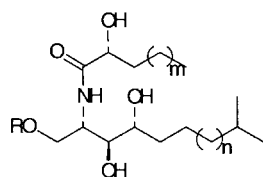
**Tunicates** – Chemical examination of the tunicate *Cystodytes cf. dellechiajei* collected in the Mediterranean Sea, off the Coast of Tunisia, yielded two homologous mixtures of ceramides [128] and cerebroside [129]. From the ceramide mixture [128], a new ceramide [130] was



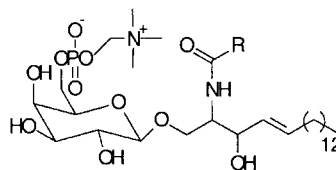


separated. The ceramide and ceramide mixture showed *in vitro* inhibition of phospholipase A2 whereas the cerebroside mixture was inactive. This is the first report of such activity for a sphingosine (Loukaci *et al.*, 2000). A novel triglycosyl ceramide, sulcaceramide, [131] has been isolated as its peracetate from the marine ascidian *Microcosmus sulcatus*. This is a rare example of a fucosylated carbohydrate moiety

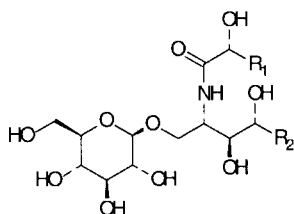
encountered as a constituent of glycosphingolipids isolated from marine invertebrates (Aiello *et al.*, 2002). The ascidian *Phallusia fumigata* collected off the Southern coast of Cadiz, Spain contains a series of new glycosphingolipids named phallusides 1-4 [132-135]. This is the first report of glycosphingolipids from an ascidian. Phallusides 1-3 contain the uncommon sphingoid base 2-amino-9-methyl-



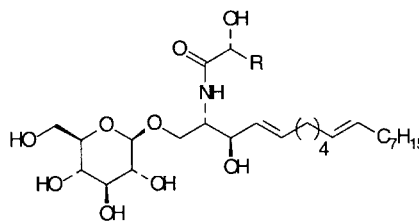
- [128] R = H; m = 17-19; n = 7-9  
 [129] R = Glucose; m = 17-19; n = 7-9  
 [130] R = H; m = 18; n = 7



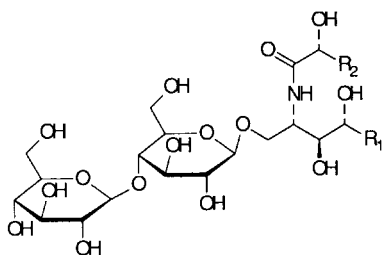
- [136] R = C<sub>16</sub>H<sub>33</sub>  
 [137] R = C<sub>15</sub>H<sub>31</sub>



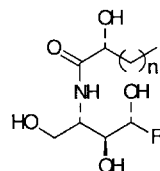
- [138] R<sub>1</sub> = C<sub>22</sub>H<sub>45</sub>; R<sub>2</sub> = C<sub>12</sub>H<sub>25</sub>  
 [139] R<sub>1</sub> = C<sub>14</sub>H<sub>29</sub>; R<sub>2</sub> = C<sub>18</sub>H<sub>37</sub>  
 [140] R<sub>1</sub> = C<sub>14</sub>H<sub>29</sub>; R<sub>2</sub> = (CH<sub>2</sub>)<sub>6</sub>CH=CHC<sub>8</sub>H<sub>17</sub>



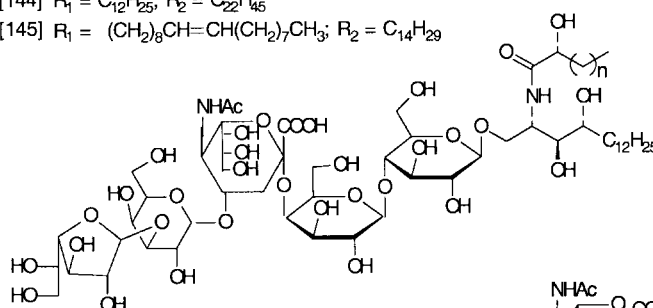
- [141] R = C<sub>20</sub>H<sub>41</sub>  
 [142] R = C<sub>21</sub>H<sub>43</sub>  
 [143] R = C<sub>22</sub>H<sub>45</sub>



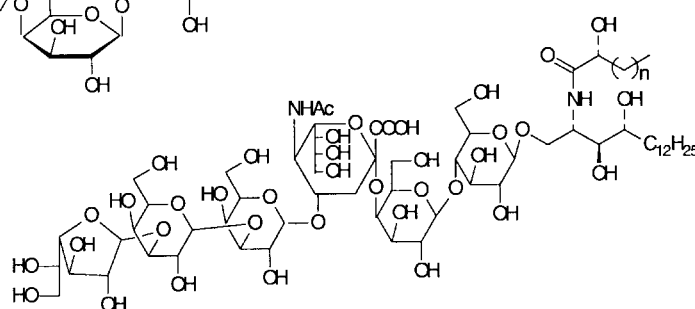
- [144] R<sub>1</sub> = C<sub>12</sub>H<sub>25</sub>; R<sub>2</sub> = C<sub>22</sub>H<sub>45</sub>  
 [145] R<sub>1</sub> = (CH<sub>2</sub>)<sub>8</sub>CH=CH(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>; R<sub>2</sub> = C<sub>14</sub>H<sub>29</sub>



- [151] n = 13; R = (CH<sub>2</sub>)<sub>4</sub>CH=CH(CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub> (Z)  
 [152] n = 20; R = C<sub>12</sub>H<sub>25</sub>  
 [153] n = 21; R = C<sub>12</sub>H<sub>25</sub>



- [146] n = 17  
 [147] n = 19  
 [148] n = 21

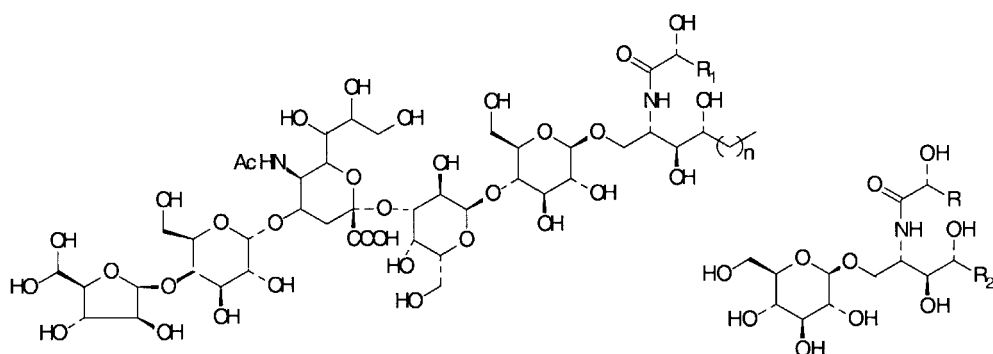
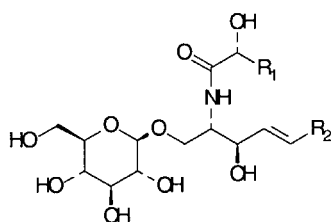
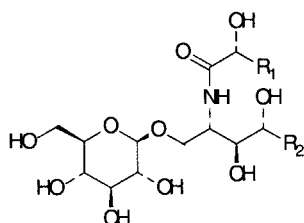
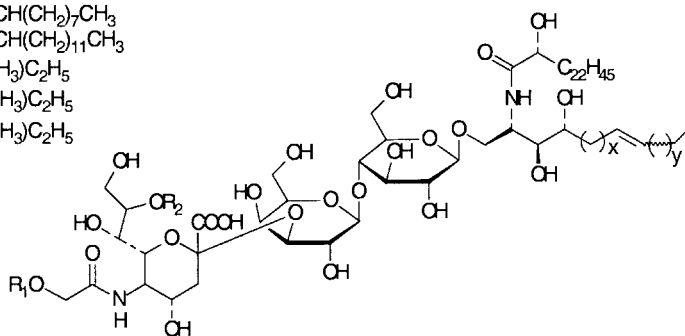
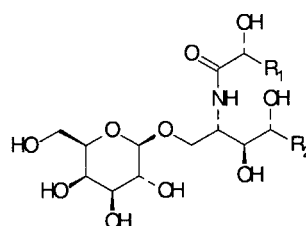


- [149] n = 19  
 [150] n = 21

D-erythro - (4E, 8E, 10E)-octadeca-4,8,10-triene-1,3-diol (Duran *et al.*, 1998). A ceramide derivative [116] was isolated from a Dayawan Bay collection of ascidian *Styela canopus* (Wang *et al.*, 2001).

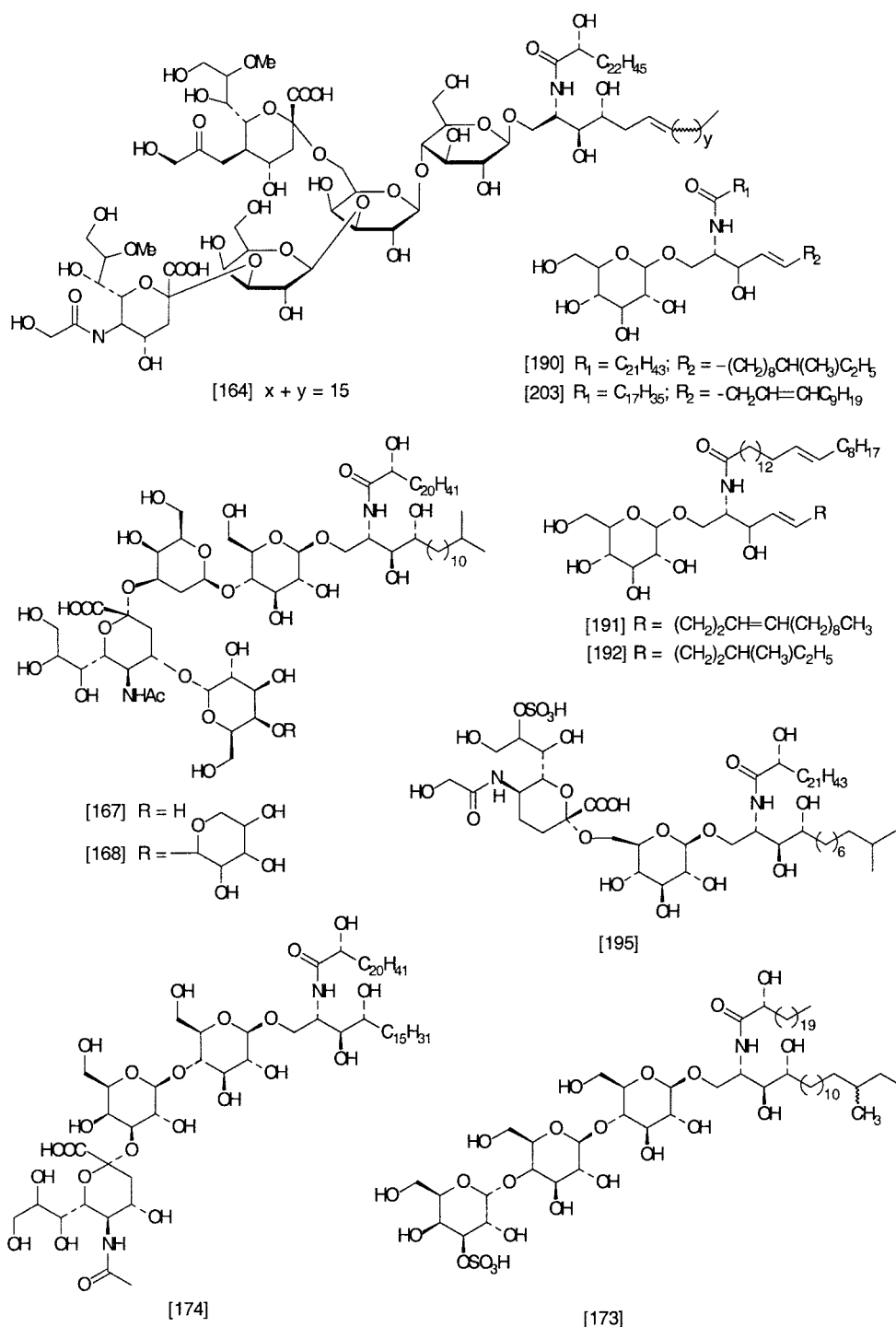
**Marine Annelid** – Two galactosyl ceramides [136, 137] carrying the phosphocholine group were isolated from a marine annelid, *Marphysa sanguinea* (Noda *et al.*, 1992).

Five monogalactosyl ceramides carrying the phosphocholine group in the galactose moiety were reported from the marine annelid, *Neanthes diversicolor* (Noda *et al.*, 1993). Neutral glycosphingolipids having fucose, xylose along with glucose and galactose, were isolated and characterized from the marine annelid, *Pseudopotamilla ocellata* (Sugita *et al.*, 1999; Itonori *et al.*, 2001).

[154]  $n = 19$ [155]  $n = 21$ [156]  $R_1 = C_{13}H_{27}$ ;  $R_2 = (CH_2)_7CH=CH(CH_2)_7CH_3$ [157]  $R_1 = C_{14}H_{29}$ ;  $R_2 = (CH_2)_7CH=CH(CH_2)_7CH_3$ [158]  $R_1 = C_{14}H_{29}$ ;  $R_2 = (CH_2)_3CH=CH(CH_2)_{11}CH_3$ [187]  $R_1 = C_{20}H_{41}$ ;  $R_2 = (CH_2)_8CH(CH_3)C_2H_5$ [188]  $R_1 = C_{21}H_{43}$ ;  $R_2 = (CH_2)_8CH(CH_3)C_2H_5$ [189]  $R_1 = C_{22}H_{45}$ ;  $R_2 = (CH_2)_{208}CH(CH_3)C_2H_5$ [165]  $R_1 = C_{14}H_{29}$ ;  $R_2 = (CH_2)_4CH=CH(CH_2)_{11}CH_3$ [166]  $R_1 = C_{22}H_{45}$ ;  $R_2 = (CH_2)_{11}CH(CH_3)_2$ [179]  $R_1 = C_{20}H_{41}$ ;  $R_2 = C_{14}H_{29}$ [180]  $R_1 = C_{21}H_{43}$ ;  $R_2 = C_{14}H_{29}$ [181]  $R_1 = C_{22}H_{45}$ ;  $R_2 = C_{14}H_{29}$ [204]  $R_1 = C_{20}H_{41}$ ;  $R_2 = (CH_2)_{12}CH(CH_3)C_2H_5$ [205]  $R_1 = C_{21}H_{43}$ ;  $R_2 = (CH_2)_{12}CH(CH_3)C_2H_5$ [159]  $R_1 = C_{13}H_{27}$ ;  $R_2 = (CH_2)_8CH=CH(CH_2)_7CH_3$ [160]  $R_1 = C_{14}H_{29}$ ;  $R_2 = (CH_2)_{11}CH(CH_3)C_3H_7$ [161]  $R_1 = (CH_2)_{12}CH=CH(CH_2)_7CH_3$ ;  $R_2 = C_{13}H_{27}$ [162]  $R_1 = C_{13}H_{27}$ ;  $R_2 = (CH_2)_4CH=CH(CH_2)_{11}CH_3$ [182]  $R_1 = C_{20}H_{41}$ ;  $R_2 = (CH_2)_{10}CH(CH_3)_2$ [183]  $R_1 = C_{22}H_{45}$ ;  $R_2 = -(CH_2)_{11}CH(CH_3)_2$ [193]  $R_1 = C_{21}H_{43}$ ;  $R_2 = -(CH_2)_9CH(CH_3)C_2H_5$ [194]  $R_1 = C_{23}H_{47}$ ;  $R_2 = -(CH_2)_9CH(CH_3)C_2H_5$ [163]  $R_1 = Me$ ;  $R_2 = H$  or  $R_1 = H$ ;  $R_2 = Me$ ;  $x + y = 15$ [184]  $R_1 = C_{20}H_{41}$ ;  $R_2 = C_{12}H_{25}$ [185]  $R_1 = C_{20}H_{41}$ ;  $R_2 = (CH_2)_{10}CH(CH_3)_2$ [186]  $R_1 = C_{22}H_{45}$ ;  $R_2 = (CH_2)_{11}CH(CH_3)_2$ 

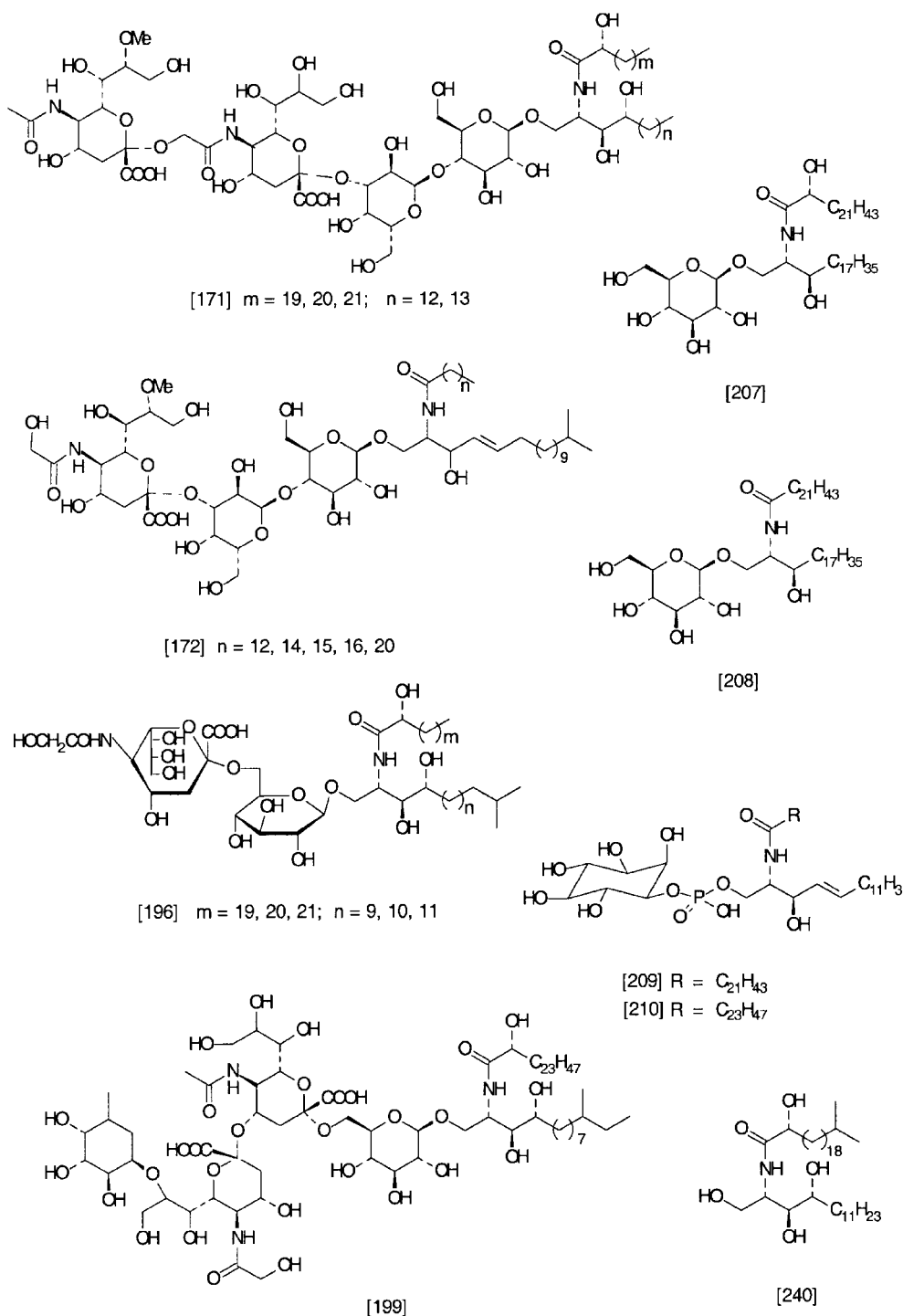
**Starfish** – Six new cerebrosides, acanthocerebrosides A-F [138-143] (Kawano *et al.*, 1988a; Sugiyama *et al.*, 1988) and two new ceramide lactosides, acanthalactosides A [144] and B [145] (Kawano *et al.*, 1988b) were isolated by using RP-HPLC from the sea star *Acanthaster planci* collected from Okinawa Island. Acanthocerebroside B [139] and C [140] were reported later from the starfish *Asterina pectinifera* (Higuchi *et al.*, 1990a) and *Asterias amurensis*

*versicolor* (Higuchi *et al.*, 1991), respectively. Five gangliosides, acanthagangliosides A-E [146-150], were obtained from the same sea star (Kawano *et al.*, 1988a; 1990). Three new phytosphingosine-type ceramides Ac-1-6 [151], Ac-1-10 [152], and Ac-1-11 [153] were isolated from the starfish *Acanthaster planci*. The position of the double bond in long-chain base was determined by mass spectra of the dimethyl disulfide derivatives of the ceramide (Inagaki *et*



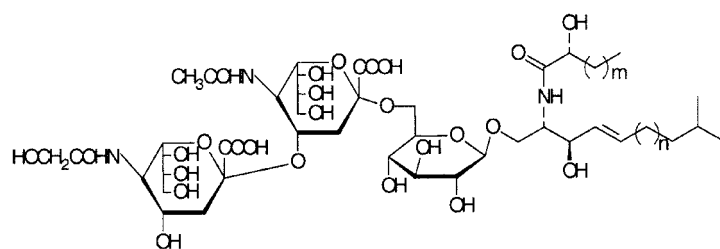
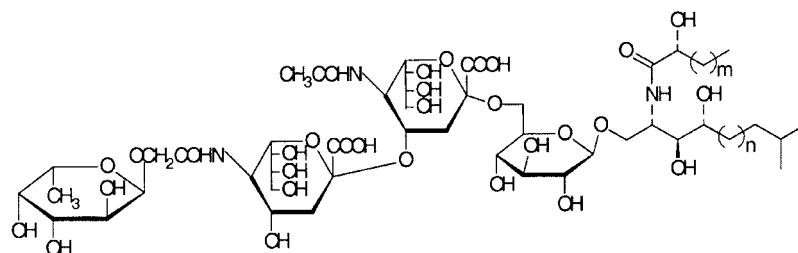
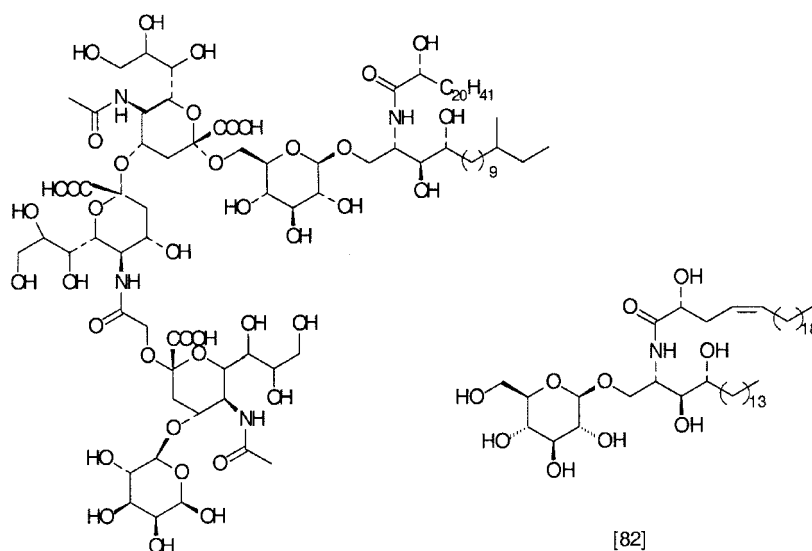
*al.*, 1998). Chemical examination of the Okinawan starfish *Acanthaster planci* furnished two new gangliosides, Acanthagangliosides I [154] and J [155]. The structures were elucidated by enzymatic hydrolysis with an *endo*-type glycosidase, which gave an oligosaccharide and homologous mixture of ceramides (Miyamoto *et al.*, 2000). Six new cerebrosides, asteriacerebrosides A-F [156-161] were isolated from the starfish *Asterias amurensis versicolor* besides two

known cerebrosides, astrocerebroside A [162] and acanthacerebrosides C [140] obtained earlier from *Astropecten latespinosus* and *Acanthaster planci*, respectively (Higuchi *et al.*, 1991). The double bond position in the cerebrosides was determined by mass spectra of their dimethyl disulfide derivatives. Two gangliosides [163, 164] were isolated from the same species of which the major ganglioside [164] showed neurotogenic and growth inhibitory activities towards



the mouse neuroblastoma cell line. These findings revealed the structure-activity relationship of gangliosides that glycosphingolipids possessing sialic acid show neuritogenic activity and gangliosides possessing terminal sialic acid are more active than that of the inner sialic acid (Higuchi *et al.*, 1993). Three new cerebroside, astrocerebroside A-C [162, 165, 166] together with a known cerebroside, acanthacerebroside A [138], were isolated from the Japanese

starfish *Astropecten latespinosus* (Higuchi *et al.*, 1990b). Further two gangliosides, LG-1 [167], and LG-2 [168], which occur as mixtures of various alkyl chains, were isolated from the same species and LG-2 showed antitumor activity against murine lymphoma L1210 cells *in vitro* (Higuchi *et al.*, 1995). From the Argentinian starfish *Cosmasterias lurida*, two new glucosylceramides [169, 170] together with a known glucosylceramides, ophiadiacerebroside E [38], were isolated

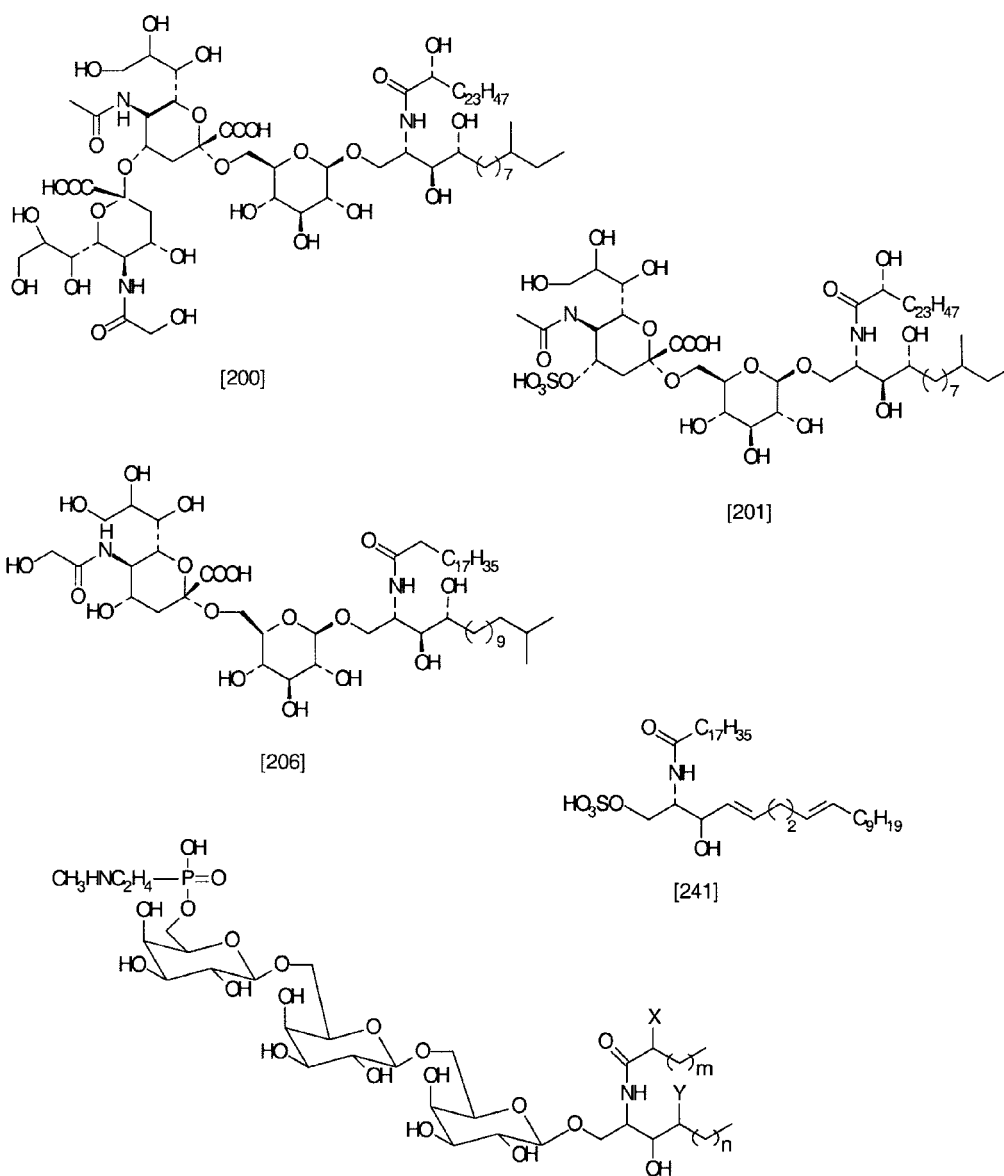
[197]  $m = 19, 20, 21$ ;  $n = 8$ [198]  $m = 19, 20, 21$ ;  $n = 9, 10, 11$ 

[202]

[82]

(Maier *et al.*, 1998). A ganglioside molecular species [171] has been obtained from the Okinawan starfish, *Linckia laevigata*. This is an unusual ganglioside that it possesses a 2→11-linked tandem-type disialosyl moiety (Inagaki *et al.*, 1999). The same species from Vietnam contained a ganglioside [172] with an 8-*O*-methyl-*N*-glycylneuramic acid residue (Smirnova, 2000a). The same residue was found in less well-defined gangliosides from the sea star *Evasterias ecinosa* (Smirnova, 2000b). A sulfatide molecular species, LMG-1, were reported from the Japanese starfish *Luidia maculata* in which [173] is the major component and exhibited neuritogenic activity towards the rat pheochromocytoma cell line, PC-12 cells (Kawatake *et al.*, 1997).

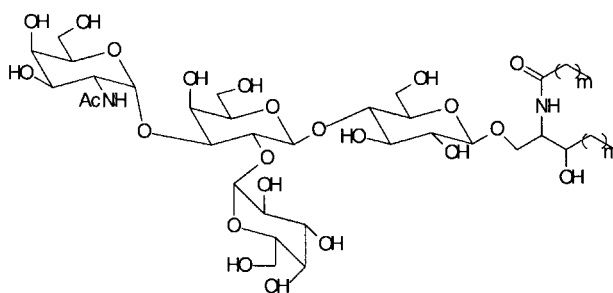
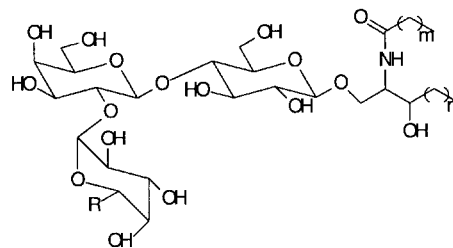
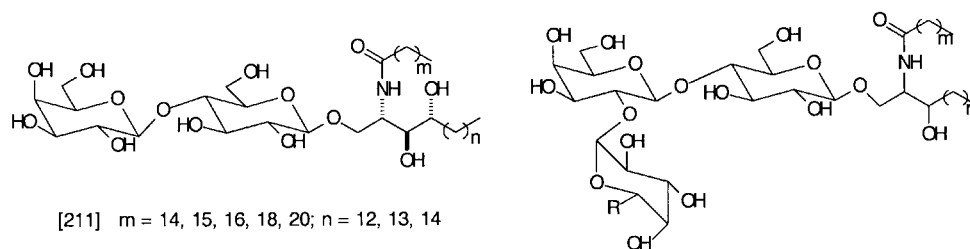
A neuritogenic ganglioside LMG-2, the major component is [174], was isolated from the same sea star, as a mixture of closely related compounds having different alkyl chains (Kawatake *et al.*, 1999). Chemical examination of the sea star *Ophidiaster ophidiumus* collected in Spain yielded five glycosphingolipids, ophidiacerebroside A-E [175-178, 38]. These compounds differs from other cerebrosides isolated from marine or terrestrial sources in that the sphingosine base, the octadecatriene, contains both a methyl branch and a conjugated diene. All the compounds showed strong cytotoxicity against L1210 leukemia cells *in vitro* (Jin *et al.*, 1994). Three new homologous glycosphingolipids, regulosides A-C [179-181] were obtained from the starfish *Pentaceraster*



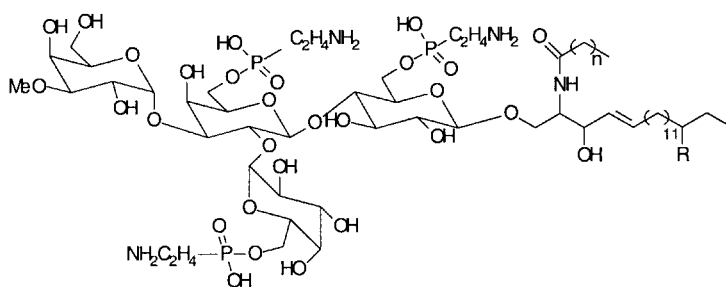
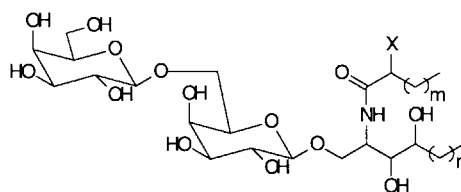
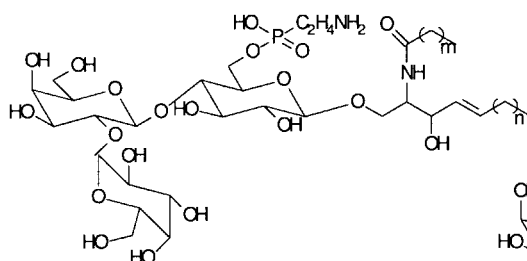
*regulus* collected on the Southern coast of India. Reguloside A showed moderate wound-healing activity (Venkannababu *et al.*, 1997). Chemical examination of the Japanese starfish *Stellaster equestris* yielded eight cerebroside [175, 178, 38, 182-186] from three cerebroside molecular species. The position of the diene system present in compounds was determined by negative-ion FAB tandem mass spectrometry (FABMS/MS) of the diol derivatives of the cerebroside (Higuchi *et al.*, 1996).

**Sea Cucumbers** – Three new sphingosine-type cerebroside, CE-2b [187], CE-2c [188], and CE-2d [189] were isolated from the Japanese sea cucumber *Cucumaria echinata* (Higuchi *et al.*, 1994a). Further five cerebroside [190-194]

and a ganglioside [195] were obtained from the same sea cucumber. The structures of these have been determined on the basis of chemical and spectral evidence. The cerebroside showed lethality towards brine shrimp whereas the ganglioside exhibited neurotogenic activity towards the rat pheochromocytoma cell line, PC-12 cells (Yamada *et al.*, 1998a). Two gangliosides were obtained from the holothurian *Cucumaria japonica* (Chekareva *et al.*, 1991). Three ganglioside molecular species, HLG-1 [196], HLG-2 [197], and HLG-3 [198] have been isolated from the Japanese sea cucumber *Holothuria leucospilota*. The ceramide moieties were composed of heterogenous phytosphingosine, sphingosine, and 2-hydroxy fatty acid units. These three



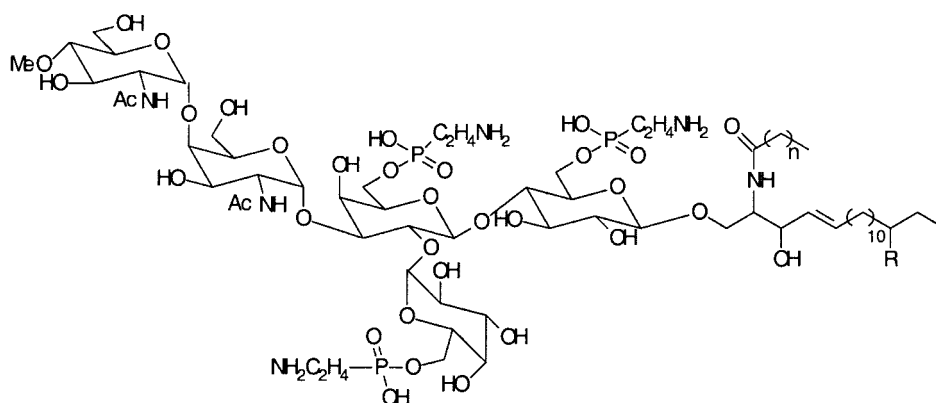
[214]  $m = 16, 17, 18, 20, 22$ ;  $n = 14, 15$



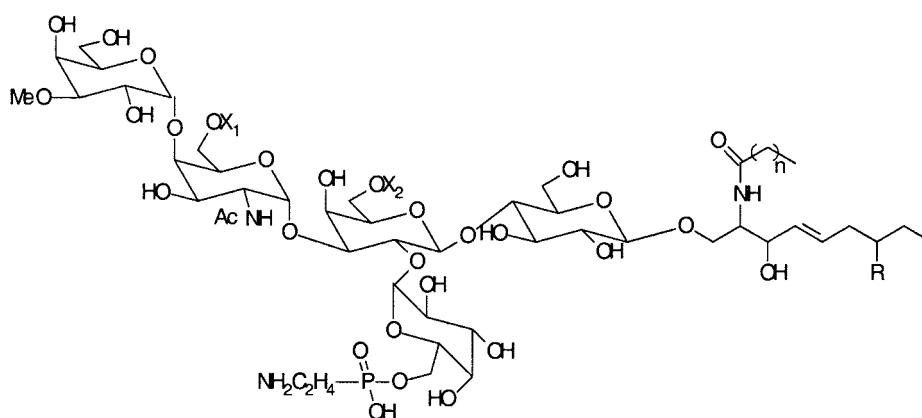
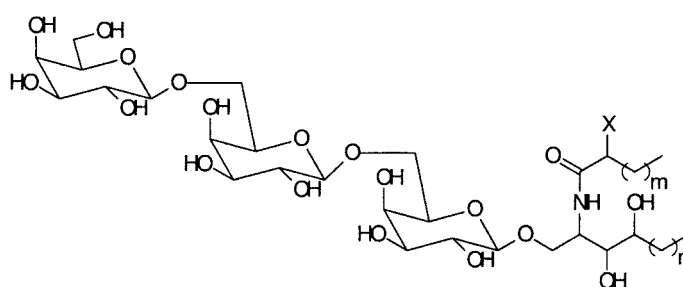
gangliosides showed neurotogenic activity towards the rat pheochromocytoma cell line, PC-12 cells, in the presence of nerve growth factor (Yamada *et al.*, 2001). Four new ganglioside molecular species, HPG-1 [199], HPG-3 [200], HPG-8 [201], and HPG-7 [202], were obtained from the sea cucumber *Holothuria pervicax*. HPG-8 is a sulfated monosialo-ganglioside, while HPG-3 and HPG-1 are disialo-

gangliosides possessing 2 → 4-linked tandem-type disialosyl moieties. HPG-7 is a trisialo-ganglioside and this is the first report of a trisialo-ganglioside from a sea cucumber. All these gangliosides showed neurotogenic activity towards the rat pheochromocytoma cell line, PC-12 cells (Yamada *et al.*, 1998b; 2000). Five cerebrosides, PA-0-1 [203], PA-0-5 [190], PA-2-5 [204], PA-2-6 [205], and CE-2c [188],





[216] SGL-I n = 14, 15, 16; R = H, Me

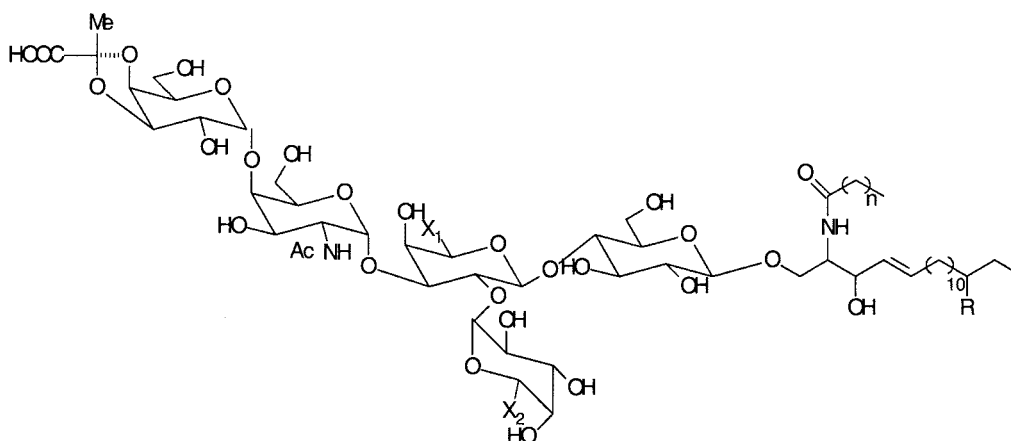
[217] SGL-II: n = 14, 16, 18; R = H, Me; X = H; X<sub>1</sub> =  $\begin{matrix} \text{OH} \\ | \\ \text{---P---C}_2\text{H}_4\text{NH}_2 \\ || \\ \text{O} \end{matrix}$ [218] SGL-I': n = 14, 15, 16; R = H, Me; X<sub>1</sub>, X<sub>2</sub> = H[219] F-21: n = 14, 16; R = H, Me; X<sub>1</sub>, X<sub>2</sub> =  $\begin{matrix} \text{OH} \\ | \\ \text{---P---C}_2\text{H}_4\text{NH}_2 \\ || \\ \text{O} \end{matrix}$ 

[227] X = H, OH; m = 14, 15, 16; n = 11, 12, 13, 19

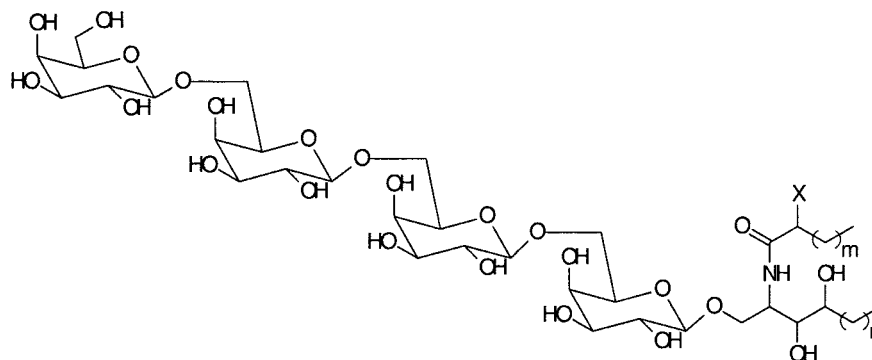
were reported from the Japanese sea cucumber *Pentacta australis* (Higuchi *et al.*, 1994b). A ganglioside molecular species SJG-1 [206] has been isolated from the sea cucumber *Stichopus japonicus*. SJG-1 possesses a sialic acid, nonhydroxy fatty acids and phytosphingosine-type long-chain bases as major ceramide components. SJG-1 exhibits neuritogenic activity toward the rat pheochromocytoma

cell line PC12 cells in the presence of nerve growth factor (Kaneko *et al.*, 1999). Additionally, a cerebroside was isolated from the same species (Hayashi *et al.*, 1990).

**Sea urchin** – Two new cerebroside, temnosides A [207] and B [208], were reported from the anti-virally active MeOH extract of the sea urchin *Temnopleurus torematicus*. This is the first report of cerebroside containing 2-amino-



- [220]  $n = 14, 16$ ;  $R = H, Me$ ;  $X_1 = -CH_2O-P(=O)(OH)-C_2H_4NH_2$ ;  $X_2 = Me$
- [221]  $n = 14, 15, 16$ ;  $R = H, Me$ ;  $X_1, X_2 = -CH_2O-P(=O)(OH)-C_2H_4NH_2$
- [222]  $n = 14, 16$ ;  $R = H, Me$ ;  $X_1 = CH_2CH_3$ ;  $X_2 = -CH_2O-P(=O)(OH)-C_2H_4NH_2$
- [223]  $n = 14, 15, 16$ ;  $R = H, Me$ ;  $X_1 = -CH_2O-P(=O)(OH)-O-C_2H_4NH_2$ ;  $X_2 = Me$
- [224]  $n = 14, 15, 16$ ;  $R = H, Me$ ;  $X_1 = -CH_2O-P(=O)(OH)-O-C_2H_4NH_2$ ;  $X_2 = -CH_2O-P(=O)(OH)-C_2H_4NH_2$



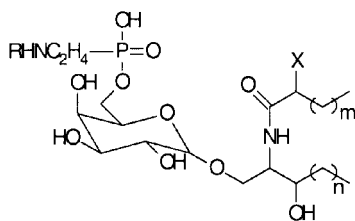
- [228]  $X = H, OH$ ;  $m = 14, 15, 16$ ;  $n = 11, 12, 13, 14$

1, 3-eicosanediol as the long chain base from natural sources (Babu *et al.*, 1997a). Ganglioside molecular species were isolated from sea urchins *Anthocardaris crassispina* (Hoshi *et al.*, 1975; Kubo *et al.*, 1990), *Echinarachnius parma* (Smirnova *et al.*, 1980), *Echinocardium cordatum* (Kochetkov *et al.*, 1976; Smirnova *et al.*, 1978), *Hemicentrotus pulcherrimus* (Kubo and Hoshi, 1990), *Strongylocentrotus intermedius* (Kochetkov *et al.*, 1973; Prokazova *et al.*, 1981), *Strongylocentrotus nudus* (Kochetkov *et al.*, 1978), and

*Tripneustes ventricosa* (Shashkov *et al.*, 1986).

**Crinoid** – Two major inositol phosphoceramides [209, 210] were isolated from the lipids of the feather star *Comanthus japonica* (Arao *et al.*, 1999). Further two novel gangliosides CJP2 and CJP3 were isolated from the same feather star (Arao *et al.*, 2001).

**Molluscs** – The sea snail *Aplysia juliana*, on chemical examination, furnished different mixtures of lactose-containing cerebrosides [211], triglycosyl ceramides [212],

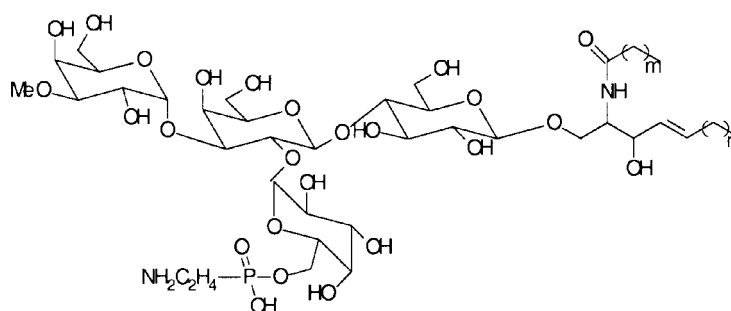


[229] R = Me; X = H, OH; m = 16, 17, 18, 20; n = 13, 14, 15

[230] R = H; X = H, OH; m = 16, 17, 18, 20; n = 13, 14, 15

[231] R = H; X = H, OH; m = 16, 17, 18; n = 19

[232] R = Me; X = H, OH; m = 16, 17, 18; n = 12, 13, 15, 19



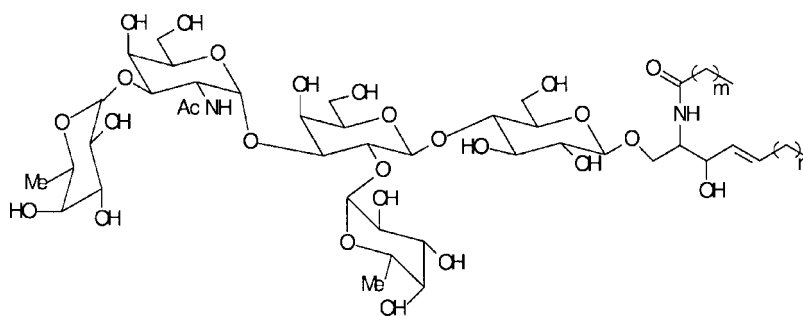
[233] m = 15; n = 12

[236] m = 16; n = 13

[234] m = 15; n = 13

[237] m = 17; n = 12

[235] m = 16; n = 12



[238] m = 14,16,18; n = 10,11,12

fucosylated triglycosyl ceramides [213], and tetraglycosyl ceramides [214] along with usual glucosyl and galactosyl ceramides (Yamaguchi *et al.*, 1992a). A phosphoglycosphingolipid [215] was also isolated from the eggs of the same organism (Yamaguchi *et al.*, 1992b).

The sea hare *Aplysia kurodai* produces a variety of phosphorus-containing glycosphingolipids: SGL-I [216], SGL-II [217], SGL-I' [218], F-21 [219], FGL-IIIb [220], FGL-V [221], FGL-IIa [222], FGL-I [223], F-9 [224], EGL-I [225], and EGL-II (Araki *et al.*, 1980; 1986; 1987a; 1987b; 1989; 1991; 1992; 2001; Abe *et al.*, 1991; Yamada *et al.*,

1995). Of these, SGL-I' was also reported from the snail *Dolabella auricularia* (Matsubara and Hayashi, 1993). FGL-I, FGL-IIa, F-9, FGL-IIIb, and FGL-V were characterized by the presence of a pyruvic acid molecule linked as a ketal to O-3 and O-4 of the terminal galactose of the oligosaccharide chain and this is the first report of its presence in an animal glycosphingolipid.

A class of glycosphingolipids, characteristic of molluscs, which contain only galactose residues with only 1 $\beta$ →6 glycosidic linkages is referred to as Gala-6 series. Chemical examination of the sea snails *Chlorostoma argyrostoma*

*turbinatum* and *Turbo cornutus* furnished a di- and a tri-galactosyl ceramide [226, 227] mixtures of the Gala-6 series whereas the first organism also yielded a tetragalactosyl analog [228] of the series. These organisms also gave usual galactosylceramides (Matsubara and Hayashi, 1981; 1986). The snail *C. argyrostoma turbinatum* gave a *N*-methyl-2-amino ethyl phosphonyl galactosyl ceramide (MAEP-galactosyl ceramide) [229] whereas 2-amino ethyl phosphonyl galactosyl ceramide and MAEP-galactosyl ceramide were isolated from *Monodonta labio* [230, 229] (Matsuura, 1979) and the muscle and viscera of *Turbo cornutus* [231, 232] (Matsuura, 1977; Hayashi and Matsubara, 1978).

Five homogeneous phosphoglycolipids [233-237] were isolated by reversed-phase HPLC from the mollusc *Dolabella auricularia* (Matsubara and Hayashi, 1993) and a difucosylated pentaglycosyl ceramide [238] was reported from the mollusc *Haliotis japonica* (Matsubara and Hayashi, 1982). Chemical examination of the viscera of the mollusc *Turbo cornutus* furnished a mixture of phosphotriglycosyl ceramides [239] (Hayashi and Matsubara, 1989).

**Miscellaneous** – One of the sexual pheromones of the hair crab *Erimacrus isenbeckii* was identified as ceramide [240], which is only one of a group of homologous ceramides (Asai *et al.*, 2000). A novel sulfated sphingolipid, hariamide [241] and a known ceramide [11] were reported from a *Zoanthus* sp. of the Indian Coast. This is the first report of a sulfated ceramide containing *N*-methyl-*N*-sphing-4, 8-diene as a long chain base from marine sources (Babu *et al.*, 1997b).

**Conclusions** – From the above listing, it may be summarised that sphingolipids or ceramides are liberally distributed as secondary metabolites in marine life. It is noted that in the sphingolipids the chain length of the sphingoid base and fatty acyl units is usually varied from C<sub>14</sub> to C<sub>30</sub>. The base commonly has 2 or 3 hydroxyl groups and may or may not possess double bonds. The fatty acyl part has one or none hydroxyl group present only on carbon next to the carbonyl function and may contain one or more olefinic bonds. In most of the glycosphingolipids of sponges, the sugar is connected to the ceramide part by an  $\alpha$ -glycosidic linkage. Gangliosides, characterized by a presence of sialic acid or acetylated neuraminic acid, were isolated only from starfishes, sea cucumbers, and sea urchins whereas they occur in all terrestrial vertebrates. The sugar part of the glycosphingolipids from marine sources frequently comprises glucose and galactose while fucose and xylose also occur in some compounds. Molluscs and annelids produce characteristic phosphorus-containing glycosphingolipids that have either phosphorylcholine or a phosphoethanolamine residue. The sphingolipids showed

interesting biological activities like antiviral, antitumor, immunostimulatory, and anti-inflammatory activities. Further investigations in this area may lead to new candidates which can be used in fighting human disorders.

### Acknowledgements

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