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Chemical and Biological Aspects of the Sponge Genus *Petrosia*, A Review

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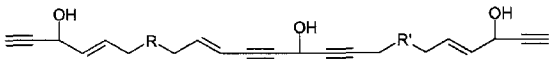
Abstract – The chemical constituents and their biological activities of the sponge genus *Petrosia* have been reviewed.

Keywords – *Petrosia*, polyacetylenes, alkaloids, steroids, biological activity.

Introduction

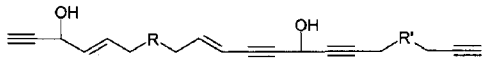
Marine natural products possess a variety of unique chemical structures that have rarely been encountered among natural products of terrestrial origin. A series of excellent reviews on marine natural products chemistry have been published by Faulkner (Faulkner, 1999), covering all the literature describing marine natural products, organized phylogenetically. A special issue of Chemical Reviews appeared in 1993 providing broad aspects of contributions as marine natural products. Literature survey revealed that the sponges have received increased attention from organic chemists, biochemists and pharmacologists as sponges yielded variety of compounds with unique structural features and high biological activity. The sponges of the genus *Petrosia* (Family: *Nepheliospongiidae*, Order: *Nepheliospongida*, Class: Demospongiae) are widely distributed throughout the tropical and subtropical waters and can be collected from intertidal zones to deep waters. To the best of our knowledge, through chemical abstracts, nine species of *Petrosia* have been subjected for chemical examination. The genus *Petrosia* is an important marine source, which yielded a various classes of bioactive molecules such as polyacetylenes, steroids and alkaloids.

Polyacetylenes and Phospholipids – Castiello *et al.* reported (Castiello *et al.*, 1980) for the first time, polyacetylenes **1** and **2** from the sponge genus *Petrosia* and Nudibranch *Peltodoros atromaculata*. The structures of **1** and **2** were partially characterized. Two polyacetylenes **3** and **4** were isolated from the sponge *P. ficiformis* found in dark caves (Cimino *et al.*, 1981). The structures of these compounds were determined on the basis of spectral data.



1. R + R' = C_nH_{2n-6}; n = 25, 26
2. R + R' = C_nH_{2n-4}; n = 28, 31, 34

3. R + R' = C_nH_{2n-4}; n = 26, 29



4. R + R' = C_nH_{2n-4}; n = 28, 31, 34

Wijekoon *et al.* isolated two new brominated demospongic acids **5** and **6** from two *Petrosia* sp. (Wijekoon *et. al.*, 1984) and their structures were elucidated with the help of CI-EI/MS and a homogeneous hydrogenation catalyst. Two high molecular weight polyacetylenes **7** and **8** were isolated from the sponge *P. ficiformis* (Cimino *et al.*, 1985). The structure elucidation of these compounds was done by the study of spectral data and chemical transformation. An antimicrobial polyacetylene alcohol, petrosynol (**9**) and its tetraketo analog petrosynone (**10**) have been isolated from the marine sponge *Petrosia* sp. (Fusetani *et al.*, 1987). The structures including absolute configuration of secondary alcohol was determined by spectral and chemical methods. Petrosynone (**10**) showed anti-microbial activity against *Bacillus subtilis*. Four high molecular weight polyacetylenes, petroformynes 1-4 (**11-14**) have been isolated from the sponge *P. ficiformis* (Cimino *et al.*, 1989). The structures of petroformynes were

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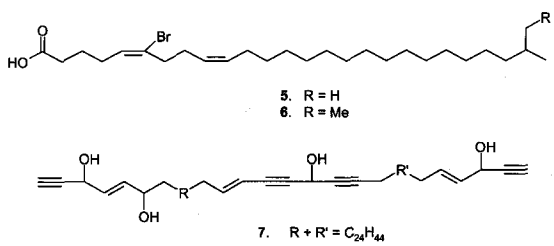


determined by means of spectral data and by chemical methods.

The same research group has isolated six novel minor polyacetylenic metabolites petroformyne B (**15**), petroformynes 6, 7 (**16**, **17**), **18-20** along with some known metabolites petroformynes 1-4 (**11-14**), petromormyne 5 (**21**) from the marine sponge *P. ficiformis* (Cimino *et al.*, 1990) by means of bioassay directed purification. Anti-tumor and potato disc assay and the assay for the inhibition of sea urchin egg development were conducted on the most abundant compounds, **11-14**. The trihydroxypoly-acetylenes **11** and **12** exhibited good anti-tumor activity. The brine shrimp (*A. salina*) lethality assay was conducted on pure compounds and it was found that these are the most potent substances ever reported in this assay (Table 1).

Two diyne enol ethers of glycerol **22** and **23** were isolated from a New Zealand sponge *P. hebes* (Perry *et al.*, 1990). The structures of these new compounds were elucidated by the study of spectral data. Very long chain and novel fatty acids **24** and **25** have been

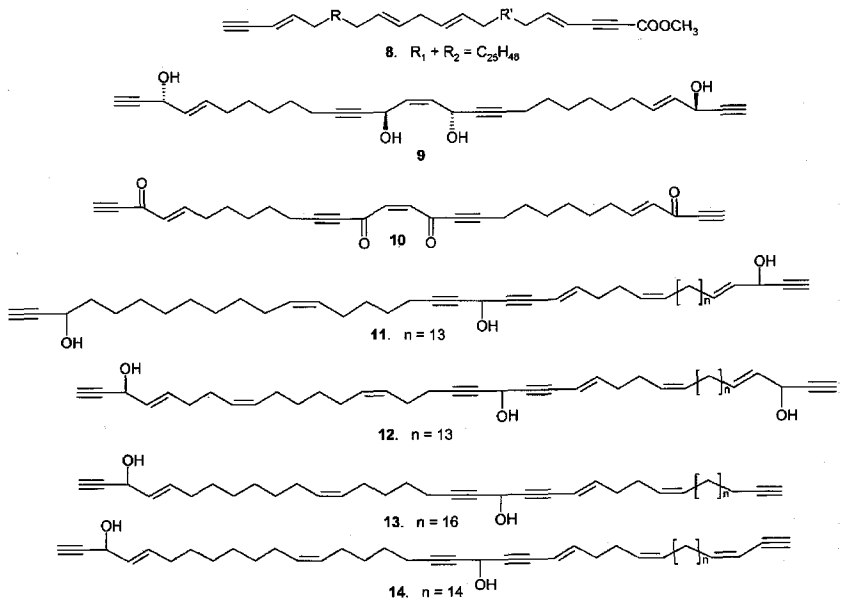
Table 1. Biological Activities of Petroformynes (**11-14**)

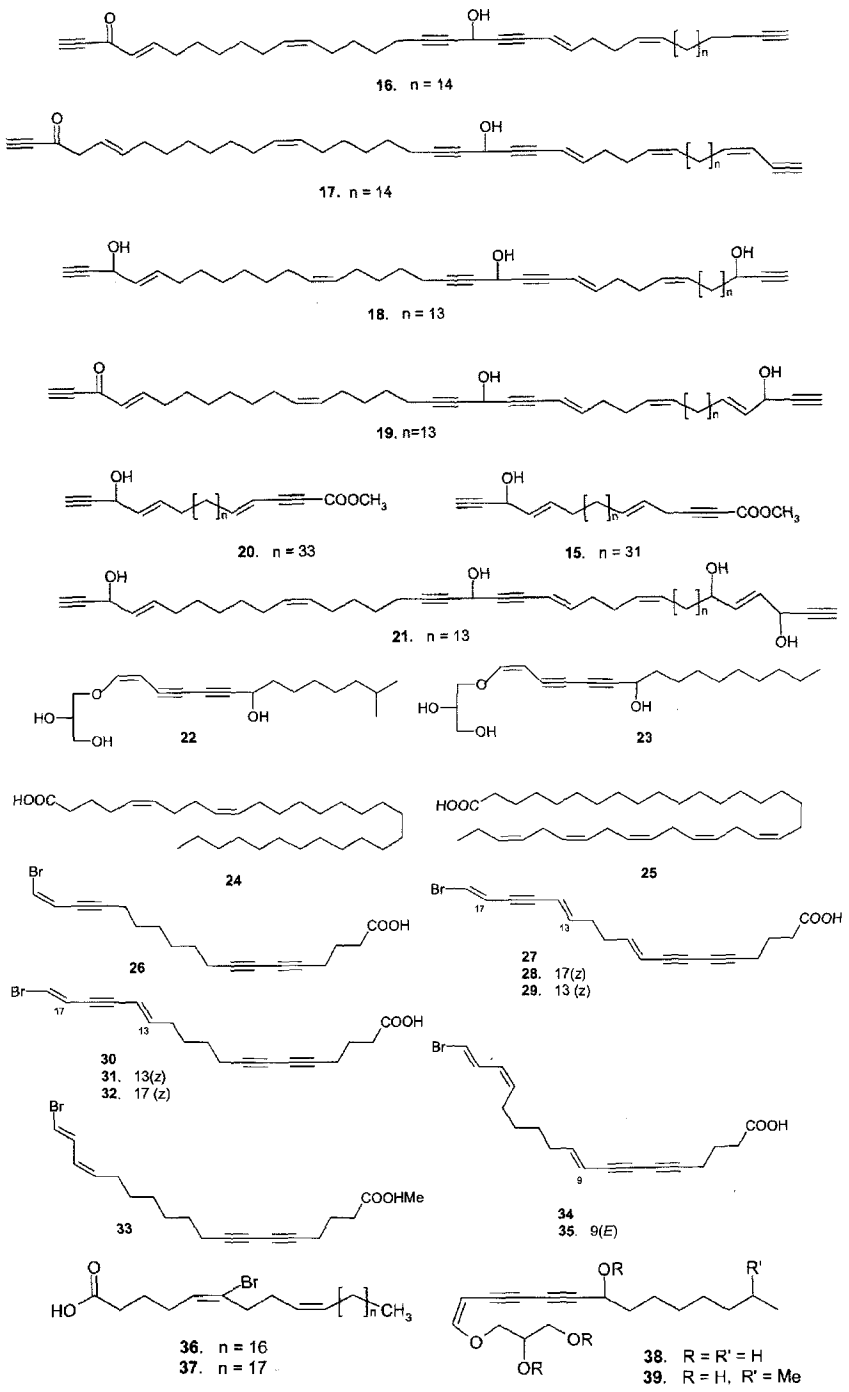
Compound	Brine Shrimp Assay LC_{50} (μg/ml)	Sea Urchin Egg Assay LC_{50} (μg/ml)	Anti-tumor Potato Disc % inhibition 0.5 (μg/ml)
11	0.014	10	35
12	0.009	1	15
13	0.003	10	49
14	0.0075	50	43

isolated from the sponge *P. pellasarca*. Structural elucidation of these compounds was done by the study of spectral data (Carballeira and Rayes, 1990). Diyne enol ethers of glycerol **22** and **23** were found to be not significantly cytotoxic against P388 cell line with ID_{50}'s > 6 and >11 μg/ml, respectively.

In 1993, Fusetani *et al.* isolated ten new brominated C-18 acetylenic acids (**26-35**) from the sponge *P. volcano* and their structures were determined by spectroscopic methods as well as comparison of spectral data with those of known related metabolites (Fusetani *et al.*, 1993). Compound **33** and related acetylenic metabolites of *P. ficiformis* showed some interesting biological properties. Brominated C-18 polyacetylenic acids (**26-35**) have shown anti-fungal activity against *Mortieralla ramanniamus*.

An unidentified species of the Caribbean sponge *Petrosia* contains two novel brominated phospholipid fatty acids **36** and **37** (Carballeira and Shalabi, 1993) and their structure elucidation was accomplished by





means of mass spectrometry and chemical transformation, including deuteration with Wilkinsons catalyst.

Two acetylenic enol ether glycerides **38** and **39** were isolated from the Okinawan marine sponge of the genus *Petrosia* (Iguchi *et al.*, 1993). The plane structure of these glycosides were deduced from spectroscopic analysis and established by enantioselective total synthesis of all possible stereoisomers. It became evident from the synthesis that the natural product **38** consisted of a mixture of (7*R*,2'*S*)-**38** (petrosyne Ia) and (7*S*,2'*S*)-**38** (petrosyne Ib) and the natural product **39** consisted of a mixture of (7*R*,2'*S*)-**39** (petrosyne

IIa) and (7*S*,2'*S*)-**39** (petrosyne-IIb). The synthetic petrosyne Ia showed moderate anti-fungal activity at a concentration of 1 μg/ml towards *Trichophyton mentagrophytes* and *Staphylococcus aureus*.

Two novel petrosynol (**40**) and petrosolic acid (**41**) were isolated from the marine sponge *Petrosia* sp. (Isaacs *et al.*, 1993) and the structure of compound **41** was determined mainly by NMR spectroscopy. Petrosynol (**40**) and petrosolic acid (**41**) were evaluated for their inhibitory potency against the various activities of HIV-1 RT, i.e., RDDP, DDDP and RNase H functions. In general, compounds **40** and **41** exhibited inhibitory activity of the DNA polymerase functions of HIV-1 RT but showed almost no inhibition of RT-associated RNase H. Compound **41** was found to be the most potent inhibitor of the RDDP activity (with 50% inhibition obtained at 1-2 μM and 95% at 5.9 μm), whereas the DDP activity was significantly less sensitive (See Table 2).

Four polyacetylenes **42-45** have been isolated from the marine sponge *Petrosia sp.* (Ochi *et al.*, 1994) and the structures of these compounds including absolute stereochemistry have been elucidated by spectral and chemical methods. The sponge *P. corticata* contained (Li *et al.*, 1994) three acetylenic acids, corticatic acids A-C (**46-48**) and their structures were determined by spectroscopic methods. Polyacetylenes **43**, **44** and **45** inhibited the cell division of fertilized ascidian (*Styela partita*) eggs with LC_{50} values of 30, 5.0 and 25 μg/ml respectively, and compounds **42**, **43** and **45** displayed toxicity in the brine shrimp lethality bioassay LC_{50} = 30, 0.1, 0.3 and 0.5 μg/ml respectively. Corticatic acids A-C (**46-48**) exhibited antifungal activity.

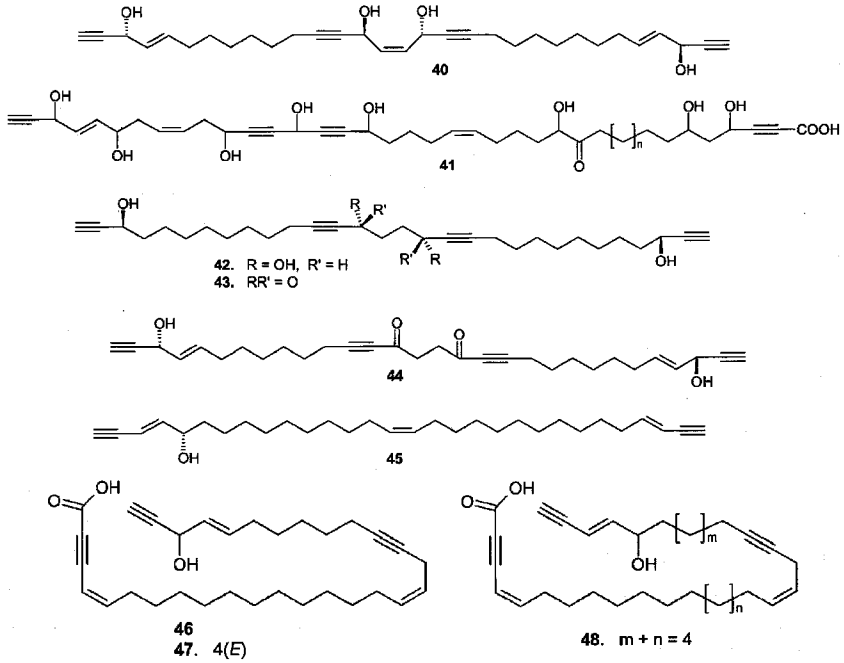
Table 2. Inhibition of HIV-1 Reverse Transcriptase-associated RDDP, DDDP and RNase H Functions by Compounds 40 and 41

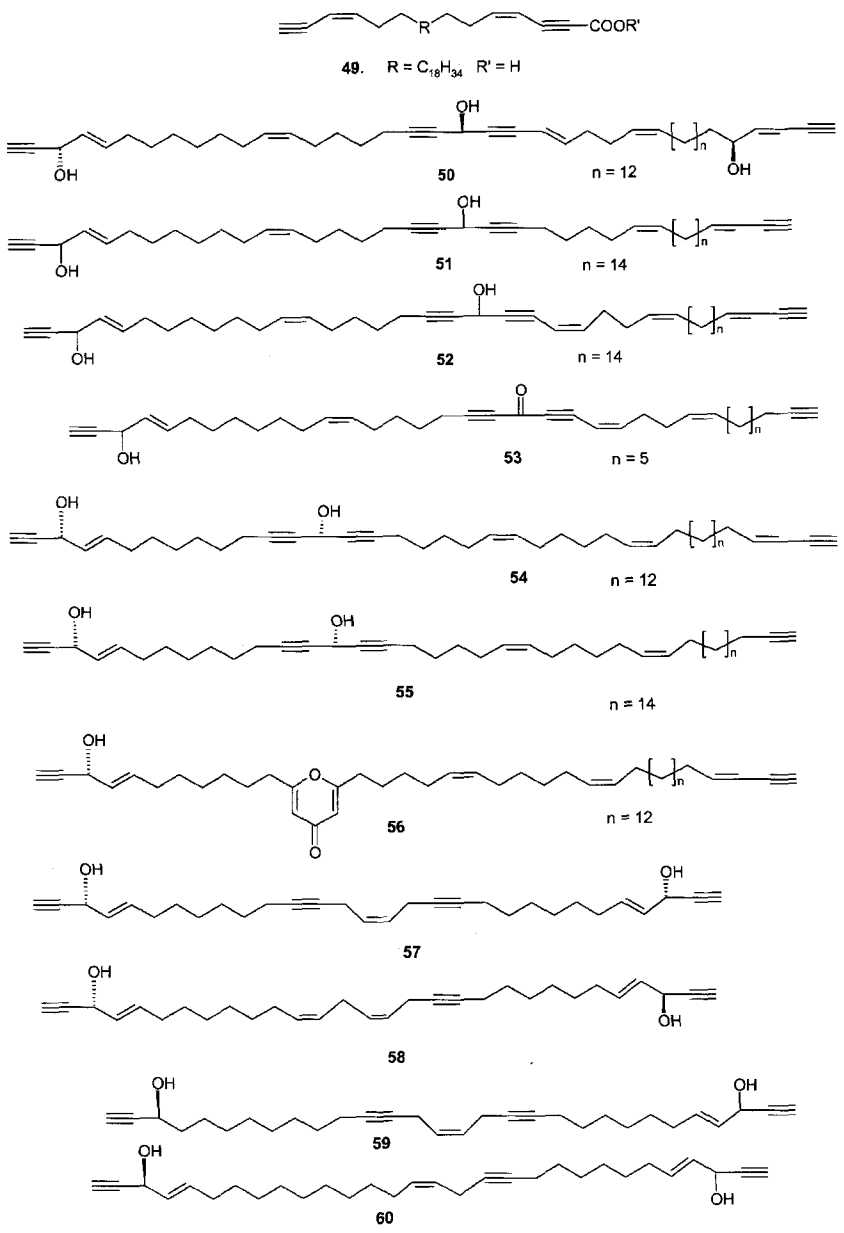
RDDP		DDDP		R Nase H	
IC_{50}	IC_{50}	IC_{50}	IC_{50}	IC_{50}	IC_{50}
15.8±0.8	38.5±0.5	36.0±2.0	74.0±3.0	>200	>>200
1.2±0.3	5.9±1.5	6.2±0.2	16.5±1.7	39.5±4.5	>>200

*The inhibitory concentration leading to 50% (IC_{50}) and 95% (IC_{50}) inhibition of the initial enzymatic activities of HIV-1 RT, expressed in M. All data represent mean values (± range) for at least two separate experiments.

Five novel polyacetylenes (**49-53**) were isolated from two different populations of the sponge *P. ficiformis* (Guo *et al.*, 1998) collected in the Mediterranean Sea and the Atlantic Ocean, and their structures were established by extensive NMR analysis and comparison with known petroformynes.

Long chain polyacetylenes petrocortynes A-C (**54-56**) and petrosiacetylenes A-D (**57-60**) have been isolated from a sponge of the genus *Petrosia* (Seo *et. al.*, 1998). Petrocortyne A (**54**) and petrocortyne B (**55**) are C_{46} linear tetraacetylenes structurally related





to petroformynes, while petrocortyne C (**56**) possesses an unusual γ-pyrone ring formed by an oxidative cyclization of diacetylenic carbinol functionality. Petrosiacetylenes A-D (**57-60**) are highly symmetric C_{30} linear polyacetylenes, and **59** and **60** were isolated as inseparable mixtures of diastereomers and the structures of these compounds have been elucidated by combined chemical and spectral methods. Absolute configuration has been determined by the modified Moshers method. Petrosiacetylenes A (**57**) and C (**59**) displayed significant toxicity (LC_{50} 0.22 and 19.9 ppm, respectively) against brine shrimp larvae while other petrosiacetylenes are not toxic (LC_{50}>300 ppm). In an inhibitory assay against RNA-based reverse transcriptase, compounds **57** and **59** totally cleaved the template 168 rRNA obtained from *Escherichia coli* at the concentration of 10 μg/20 ml while other compounds did not cleave it at all. On the other hand, all of the petrocortynes and petrosiacetylenes including **57** and **59** did not cleave a super-coiled DNA (PVC 119) at the same concentration.

In other enzyme inhibitory activities, compounds

58 and **59** displayed moderate inhibition (49 and 36%, respectively) against PLA2 at the concentration of 50 μg/ml, while other petrosiacetylenes were much less active (20 and 23% for **57** and **60**, respectively). Among those petrocortynes, the γ-pyranose-containing **56** was significantly more active (42%) than others (31 and 17% for **54** and **55**, respectively). Similarly, compounds **56**, **58** and **59** exhibited weak inhibition (22, 26 and 25%, respectively) against Na^+/K^+ ATPase at the concentration of 20 μg/ml, while other compounds were not active.

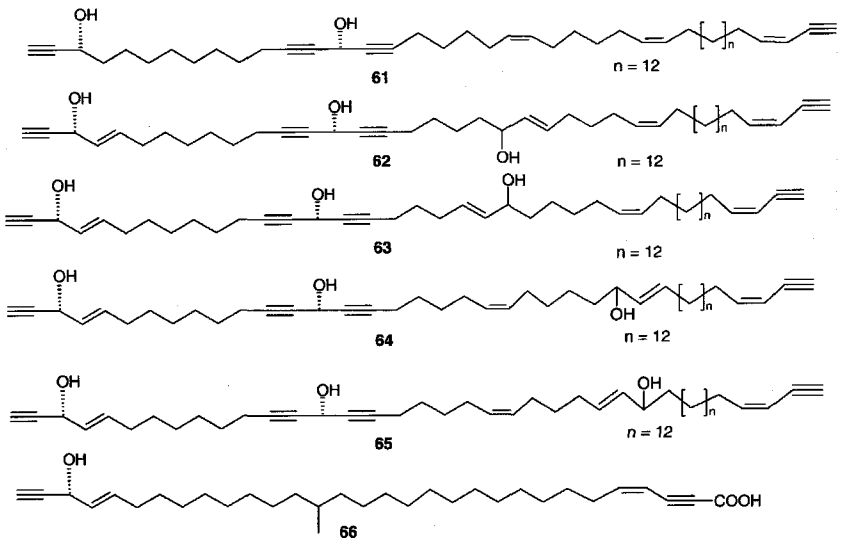
Five new C_{46} polyacetylenes petrocortynes D-H (**61-65**) were isolated from a sponge of the genus *Petrosia* collected from Komun Island, Korea (Shin *et al.*, 1998). Petrocortyne D (**61**) is a 4,5-dihydro derivative of a diastereomer of petrocortyne A (**54**) and petrocortynes E-H (**62-65**), which possess an additional allylic hydroxyl group. The structures of these compounds were determined by combined chemical and spectral methods and absolute configuration of most of the asymmetric carbon centers were determined by the modified Mosher's method. Petrocortynes D-H (**61-65**) exhibited moderate cytotoxicity against a human leukemia cell line (K-562) having LC_{50} values of 45, 7, 21, 30 and 11 μm, respectively. In addition, **62-65** inhibited PLA2 at a concentration of 50 μg/ml by 48, 25, 36 and 32%, respectively.

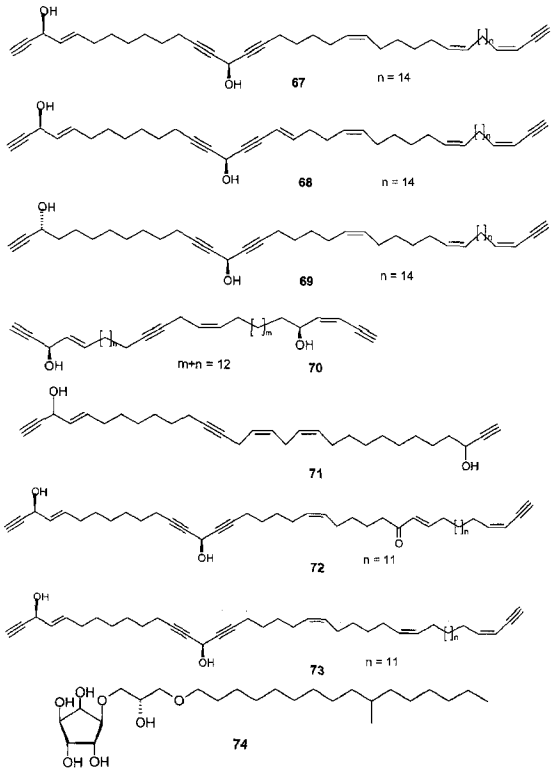
A new polyacetylene, aztequynol A (**66**) (Guerriero *et al.*, 1998) has been isolated from the nepheliospongid sponge *Petrosia sp.* collected from the Banc Azteque off New Caledonia, which represents the first case of a structurally defined C-branched polyacetylene, based on high-energy collisionally activated decomposition tandem mass spectrometry of lithium adducts which may have wide application in natural product structural analysis.

Three C_{46} (**67-69**) and two C_{30} (**70-71**) polyacetylene alcohols, (3*S*,14*S*)-petrocortyne A (**67**), petrotetrayndiols A-B (**68-69**), and dideoxypetrosynols E-F (**70-71**) (Kim *et al.*, 1999b) have been isolated along with petrosiacetylene D from the marine sponge *Petrosia* sp. collected near Komun Island, Korea. Compound **67** was identified as the stereoisomer of petrocortyne A and the remaining structures (**68-71**) were established by spectral methods. The stereochemistry of these compounds was determined by modified Moshers method. All these compounds have shown cytotoxic activity against human solid tumor cell lines.

Two new polyacetylene alcohols with a C_{45} carbon skeleton (**73**) and with an enone moiety in the alkyl chain (C_{46}, **72**) (Lim *et al.*, 1999) were isolated from the marine sponge *Petrosia* sp. These two compounds have displayed considerable cytotoxicity against human solid tumor cell lines. Significant inhibition on DNA replication by **72** and **73** was also observed which could be explanatory of their cytotoxicity. A cyclitol derivative (**74**) (Kim *et al.*, 1999a) was isolated from the Korean marine sponge *Petrosia* sp. This (**74**) has shown inhibition on simian virus 40 (SV40) origin-dependent DNA replication *in vitro*.

Four new polyacetylenes (**75-78**) (Kim *et al.*, 1998) having structural features related to duryne and petrosynol were isolated from *Petrosia* sp. from





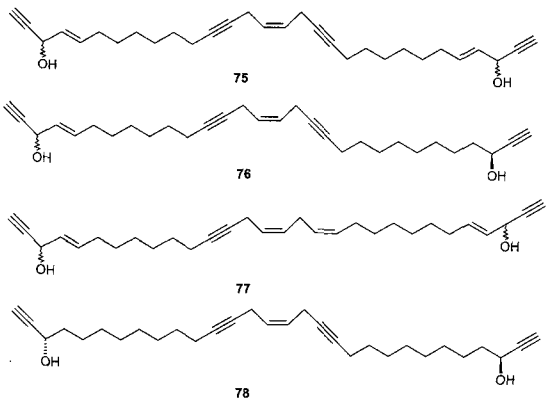
the Korean waters. All the compounds have shown moderate to significant cytotoxic activity against human tumor cells (A 549, SK-OV-3, SK-MEL-2, XF 498, HCT 15). Among all these, **75** was the most potent in all five cell lines, while **77** was the least potent.

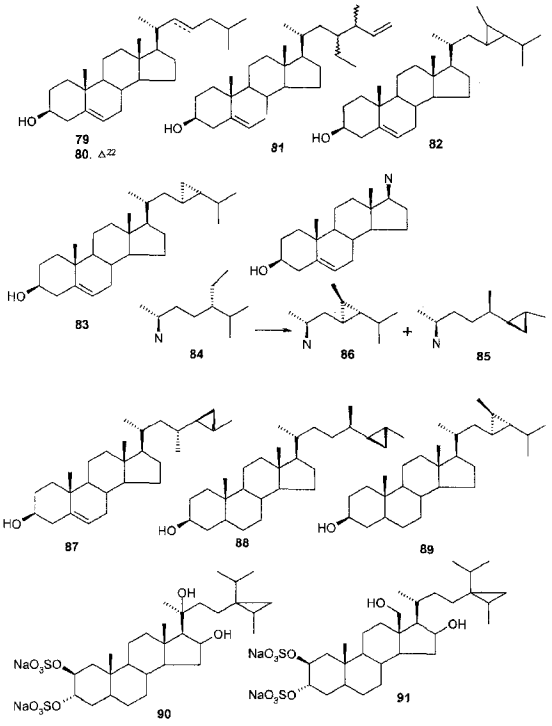
Steroids – Kanazawa *et al.* reported that cholest-5-en-3β-ol (**79**) and cholesta-5,22-dien-3β-ol (**80**) were the major sterols present in the sponge *Petrosia* (Kanazawa *et al.*, 1979).

A biosynthetically unprecedented sterol ficisterol (**81**) has been isolated from the marine sponge *P. ficiformis* and the structure was elucidated on the basis of spectral studies and by semi-synthesis (Khalil *et al.*, 1980). A major sterol with a cyclopropane in the side chain, petrosterol (**82**) has been isolated from the sponge *P. ficiformis* (Sica and Zollo, 1978) and the structure was determined by the study of spectral data and chemical transformations. Later the crystal structure of petrosterol *p*-bromobenzoate was reported (Mattia *et al.*, 1978). A minor sterol **83**, with cyclopropane in side chain has been reported from the sponge *Petrosia* (Proudfoot and Djerassi, 1984) and the structure was elucidated on the basis of spectral data and by synthesis.

Twelve sterols possessing the rare 5β-dihydro nucleus were isolated from the marine sponge *P. ficiformis*. These sterols have not previously been encountered in any samples of *P. ficiformis* and appear to be the result of bacterial metabolism of the endogenous sponge sterols (Seidel *et al.*, 1986). First time a saturated alkyl group has been enzymatically converted to a cyclopropane. When clionasterol (**84**) was fed to *P. ficiformis* (Giner *et al.*, 1990), 40% of the clionasterol (**84**) was converted to petrosterol (**85**) and dihydrocalysterol (**86**).

Three new cyclopropane-containing sterols hebesterol (**87**), petrostanol (**88**) and 23,24-dihydro-5α-calystanol





(**89**) have been isolated from the sponge *P. hebes*, together with the known principal sterol petrosterol (**85**) (Cho and Djerassi, 1987).

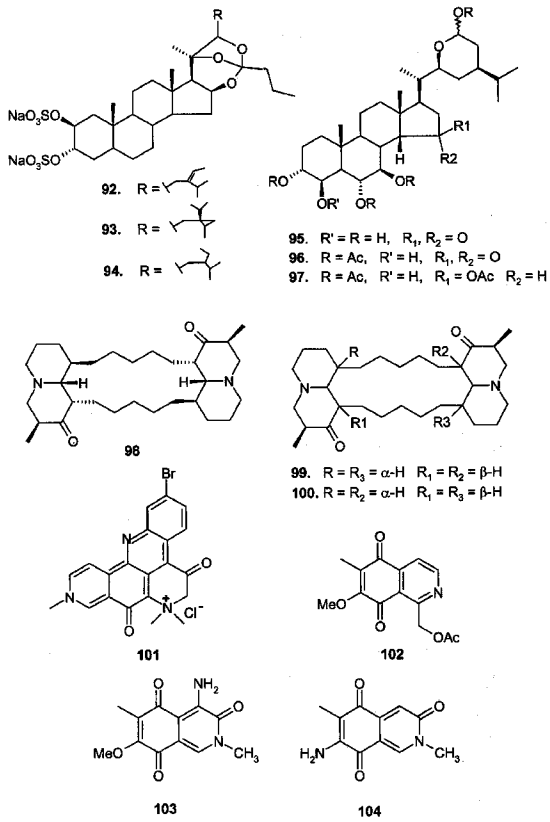
Two novel sterols weinbersterol disulfates A (**90**) and B (**91**) were isolated from the sponge *P. weinbegi* (Sun *et al.*, 1991) and the structures of these two sterols were assigned mainly on the basis of spectral data. Weinbersterol disulfates A (**90**) and B (**91**) exhibited *in vitro* activity (EC_{50} = 4.0 and 5.2 μg/ml, respectively) against the feline leukemia virus (FeLV), and compound **86** also showed activity against the human immunodeficiency virus (EC_{50} = 1.0 μg/ml).

Three new anti-viral sterol disulfate *ortho* esters **92-94** were isolated from the marine sponge *P. weinbergi* and the structures of these compounds were elucidated mainly by spectroscopic data (Koehn *et al.*, 1991). The sterols **92-94** exhibited anti-viral activity.

A highly oxygenated steroid with an 'unusual' 14β-configuration contignasterol (**95**) was isolated from the marine sponge *P. contignata* (Burgoyne *et al.*, 1992) and the structure of contignasterol was elucidated *via* spectroscopic studies of its tetraacetate **96** and its reduction product pentaacetate **97**.

Alkaloids – Petrosin (**98**), the first member of a new class of bis-quinolizidine alkaloid containing C-16 macrocycle, was isolated from the sponge *P. seriata* (Braekman *et al.*, 1982) and its structure was determined by X-ray diffraction analysis. Subsequently two new bis-quinolozidine alkaloids, petrosin A (**99**) and petrosin B (**100**), which are stereoisomers of the previously isolated petrosin (**98**), were isolated from the sponge *P. seriata* (Braekman *et al.*, 1984) and the structures of **99** and **100** were determined from their ^{1}H- and ^{13}C-NMR spectral data.

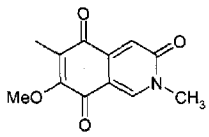
In 1988, Molinski *et al.* isolated a novel pigment, petrosamine (**101**) from the marine sponge *Petrosia sp.* (Molinski *et al.*, 1988) and the structure of petrosamine (**101**) was determined by the study of spectral data and by X-ray crystallography. A new isoquinolinequinone alkaloid, *O*-demethyl renierol acetate (**102**) was isolated from the sponge *Petrosia* sp. And the structure of new compound was determined by ^{1}H-NMR and mass spectral data (Venkateswarlu *et al.*, 1993). Two new isoquinoline alkaloids, 4-aminomimosamycin (**103**) and 7-amino-7-demethoxy-mimosamycin (**104**) along with mimosamycin (**105**) were isolated from the sponge *Petrosia* sp. and the structures of these two new compounds were



elucidated by means of spectral data (Kobayashi *et al.*, 1994). Mimosamycin (**105**) showed aldose reductase inhibitory effect (34.5%) at 10 μmol·dm^{-3}, while 7-amino-7-demethoxymimosamycin (**104**) showed cAMP phosphodiesterase inhibitory effect (26.3%) at 100 μmol·dm^{-3}.

Two new alkaloids 1,2,3,4-tetrahydro-2-*N*-methyl-8-hydroxymanzamine A (**106**) and 1,2,3,4-tetrahydro-8-hydroxymanzamine A (**107**) have been isolated from Papua New Guinea sponges of the genera *Petrosia* and *Cribochaline*, which are in different families of the order Haplosclerida and their structures were elucidated by the study of spectral data (Crews *et al.*, 1998). The new alkaloid **107** was cytotoxic to leukemia cell line P388 and exhibited an ED_{50} of 0.8 μg/ml.

Two phenyl guanidine derivatives, 7,8-dihydrotubastrine (**108**) and 4-deoxy-7,8-dihydrotubastrine (**109**), along with the sterol xestobergsterol A (**110**) were isolated from the marine sponge *P. contignata* (Sperry and Crews, 1998), and the structures of new compounds were elucidated based on spectroscopic data and comparison to the literature properties for semisynthetic **108**. This is the first example from this



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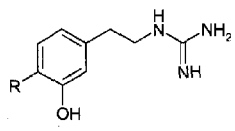
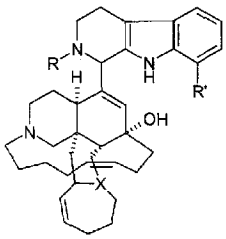
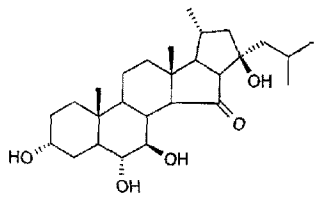


108. R = OH
109. R = H



106. R = Me X = NH+ R' = OH
107. R = H X = N R' = OH



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compound class with a saturated acyclic C_2 unit.

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