Marine Natural Products

Third year students

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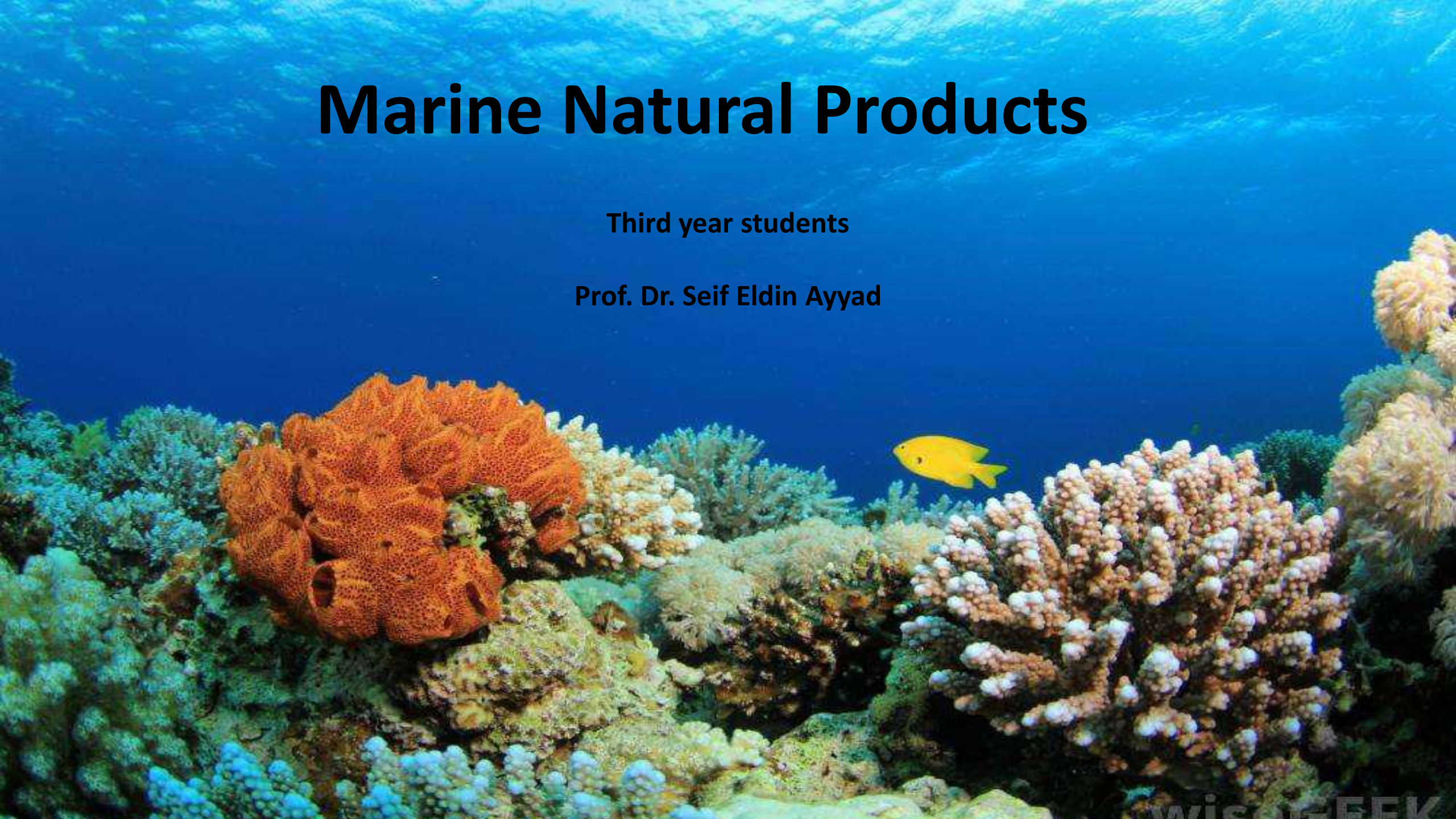

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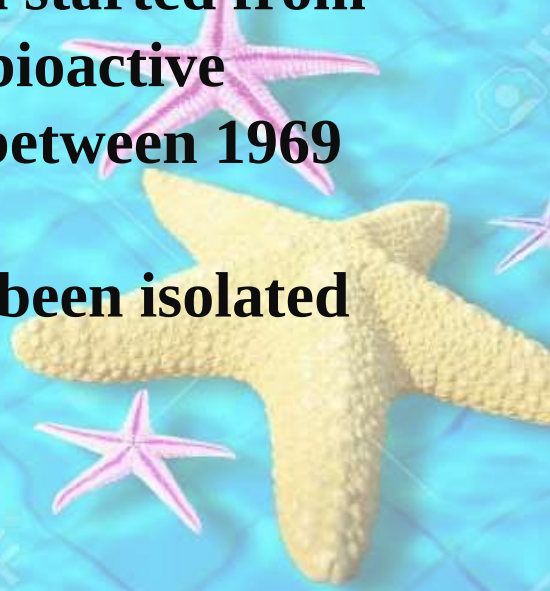
INTRODUCTION

- **The marine resources are nowadays widely studied because of numerous reasons.**
- **One of the reason is as the oceans cover more than 70% of the world surface and among 36 known living phyla, 34 of them are found in marine environments with more than 300000+ known species of fauna and flora.**
- **The attention of finding drug from sea had started from 1970s. For instance, about 300 patents on bioactive marine natural product have been issued between 1969 and 1999.**
- **So far, more than 10,000 compounds have been isolated from marine organism**



Advantages

Marine natural products are used for treatment of several diseases like

- **Anti inflammatory drugs**
- **Anti fungal drugs**
- **Anti cancer drugs**
- **Cardio vascular drugs**
- **Anti viral drugs**
- **Anti helminthetic drugs**
- **Anti parasitic drugs**
- **Anti bacterial drugs .**

Limiting factors for development of marine drugs

- Supply (sustainable, industrially feasible)
- Formulation (suitable for clinical use)
- Analytical method & preclinical PKs
- Pharmacogenetics (metabolic pathway)
- Therapeutic index
- Toxicities (Xeno)

Drugs of marine origin:

Compound Name	Source	Chemical Class	Company	Disease Area	Status
Compounds targeting ion channels					
Ziconotide (Prialt™)	Cone snail	Peptide	Elan	Chronic pain	FDA approved 2004, now marketed by Eisai in the EU
GTS-21	Nemertine worm	Anabaseine-derivative	NIMH (U. Colorado)	Schizophrenia	Phase II (Academic) completed
GTS-21	Nemertine worm	Anabaseine-derivative	Comentis	Alzheimer/ ADHD	Phase II
Compounds targeting enzymes					
Protein kinase inhibitors					
Bryostatin-1	Bryozoan	Polyketide	NCI	Cancer	No current clinical trials. Potential interest in Alzheimers
Proteasome inhibitor					
NPI-0052	Bacteria (Actinomycete)	Beta-lactone-gamma-lactam	Nereus	Cancer	Phase I

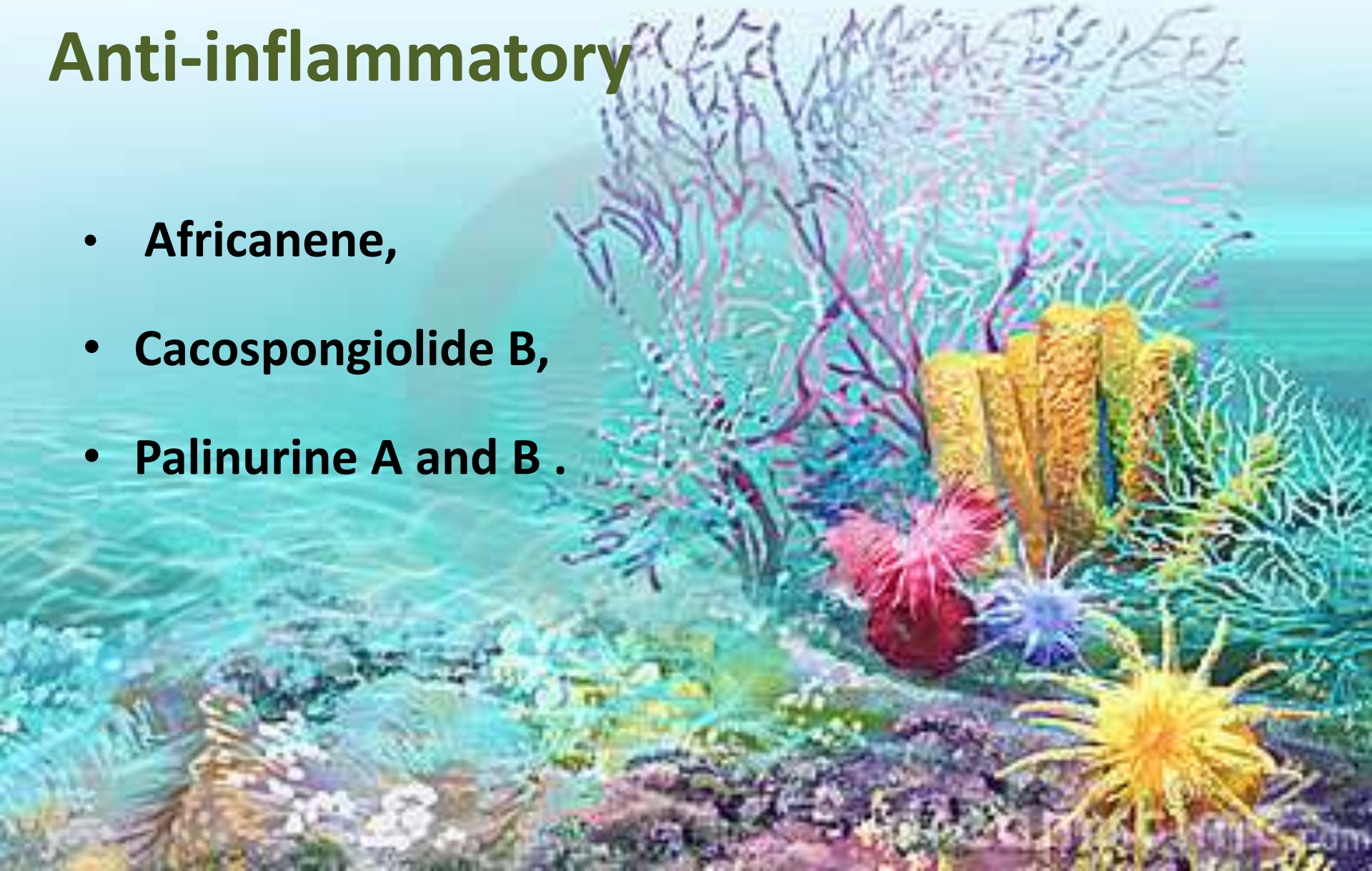
Microtubule-interacting agents

Dolastatin-10	Sea slug	Peptide	NCI/Knoll	Cancer	No details shown on NCI site after 2004
ILX-651	Sea slug	Peptide	Genzyme	Cancer	Preclinical as 4/2008, oral formulation being developed
E7389(eribulin)	Sponge	Halichondrin B analog	Eisai	Cancer	Phase III for breast cancer USA & EU; Phase II (USA) NSCLC; Phase II (US/EU) prostate, Phase II (EU) sarcoma
NPI-2358	Fungi	Diketopiperazine	Nereus	Cancer	Phase II
TZT-1027(Soblidotin) aka YHI-501	Sea slug	Peptide	Aska Pharmaceuticals	Cancer	Phase I - III (possibly). Linked to monoclonals (Auristatin PE).
E-7974	Sponge	Tripeptide	Eisai	Cancer	Phase I

DNA and transcription interactive agents					
Ecteinascidin-743-Trabectedin (Yondelis®)	Sea squirt	Tetrahydroisoquinolone alkaloid	PharmaMar/ Johnson & Johnson	Cancer	Approved by EMEA Sept 2007 Phase III ovarian cancer completed file FDA/EMEA Fall 08 December 2008 Phase II prostate cancer ongoing Phase II breast/lung cancer ongoing
PM00 104 (Zalypsis®)	Mollusc/Sponge	Synthetic alkaloid based on Jorumycin	PharmaMar	Cancer	Late Phase I development
VEGF interacting agent					
Plitidepsin (Aplidin®)	Sea squirt	Cyclic depsipeptide	PharmaMar	Cancer	Phase II multiple myeloma completed Phase II in T-NHL ongoing Combination studies ongoing

Lysosomotropic and ErbB interacting agent					
Kahalalide F	Sea slug/Algae	Cyclic depsipeptide	PharmaMar	Cancer	Phase II completed in solid tumors. Evaluated in severe psoriasis
PM02734 (Irvalec®)	Sea slug	Depsipeptide	PharmaMar	Cancer	Phase I ongoing Phase I/II in combination with Erlontinib in lung under implementation
Compounds with unknown mechanism of action					
IPL-512602	Sponge	Steroid	Inflazyme/ Orexo pharmaceuticals	Inflammation/ Asthma	No further information available. Probably discontinued
Compounds targeting GPCRs					
Pseudopterosin A-methyl ether (TMO)	Soft Coral	Diterpene glycoside	Terosin Group Inc./Univ. of CA	Wound Healing	Phase II

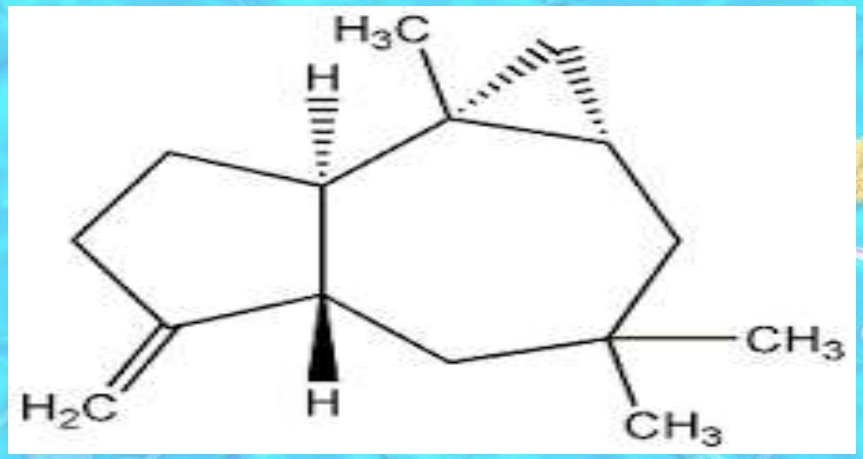
Anti-inflammatory



- Africanene,
- Cacospongiolide B,
- Palinurine A and B .

Africanene

- **Sesquiterpene africanene, isolated from the soft coral *Sinularia leptoclados***
- **It resulted in a more potent reduction of paw volume than that produced by 100 mg/kg body weight of ibuprofen, in carrageenan-induced rat edema assay**



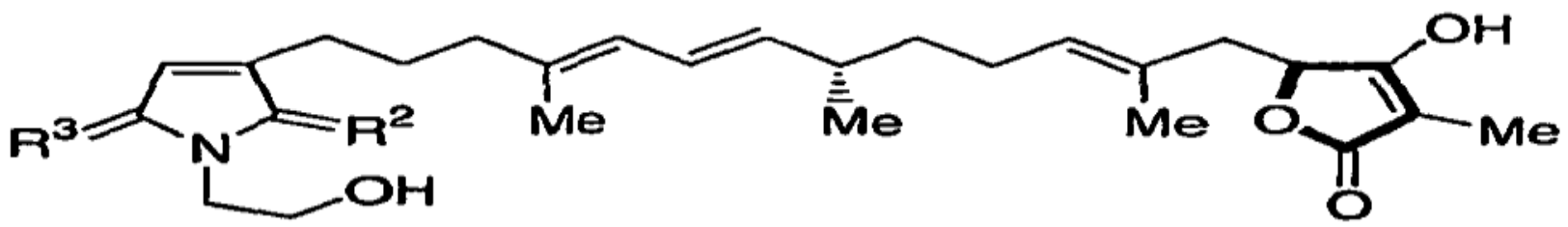
Cacospongionolide B

- **A novel sesterterpene inhibitor of human synovial phospholipase A2 isolated from the sponge *Fasciospongia cavernosa***
- **It irreversibly inhibited both secretory PLA2 in vitro and group II secretory PLA2 in vivo .**

Cacospongionolide B

Palinurine A & B

- Isolated from the marine sponge *Ircinia echinata* .
- Palinurin inhibited TXB_2 & Oxide radicals .
- Palinurine A and B were relatively ineffective inhibitors of both TXB_2 and Oxide radicals .



Palinurines

$R^2 = H_2, O; R^3 = H_2, O$

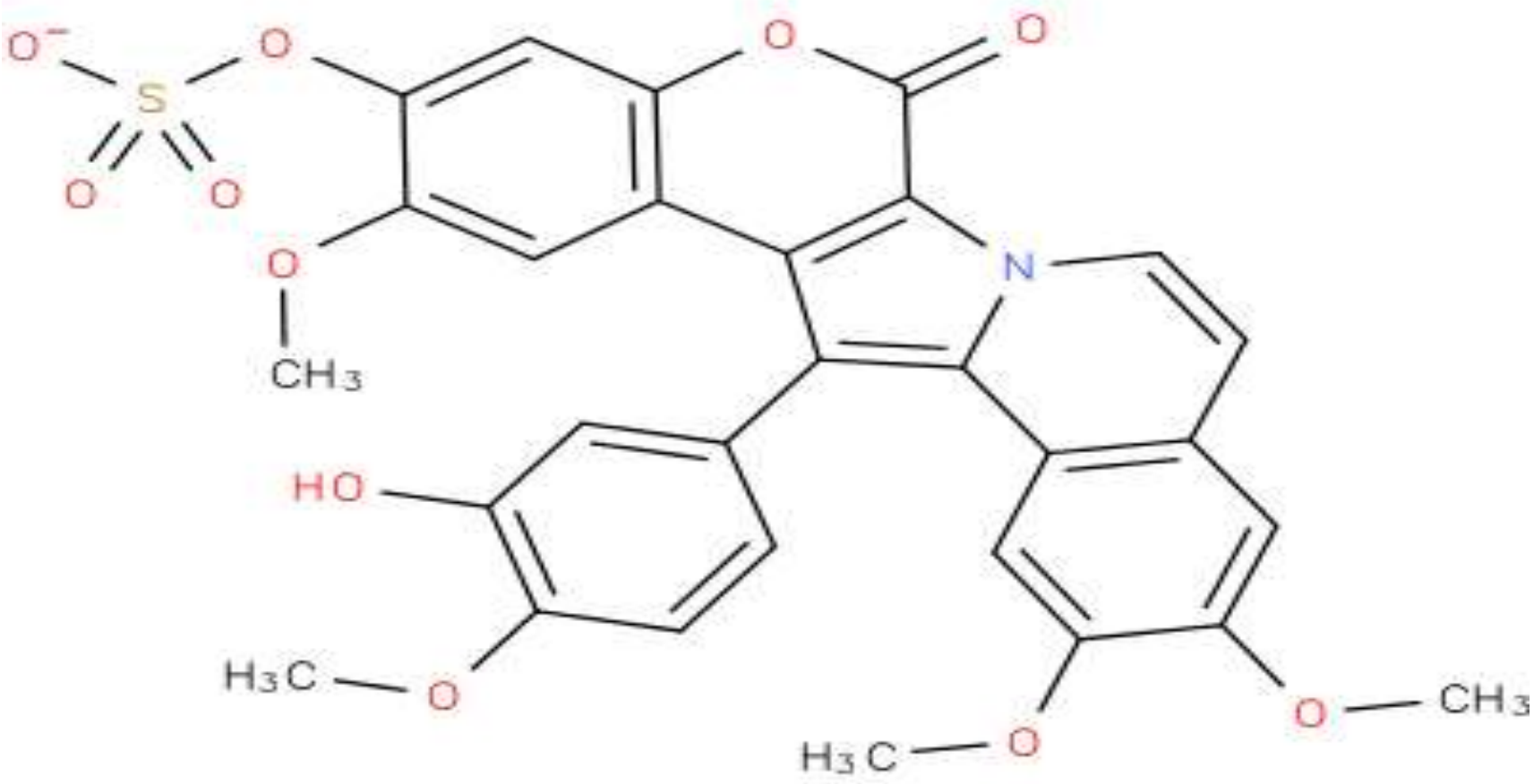
Anti-virals

- Lamellarin α-20-sulfate
- Papuamides A–D
- Polycitone A
- Glycosaminoglycan
- Sulfated β-galactan

Lamellarin α-20-sulfate

- Alkaloid lamellarin α 20-sulfate in an unidentified ascidian showed selective *in vitro* inhibition of HIV-1 integrase.
- Lamellarins form a group of more than 30 poly aromatic pyrrole alkaloids isolated from diverse marine organisms, mainly ascidians and sponges .

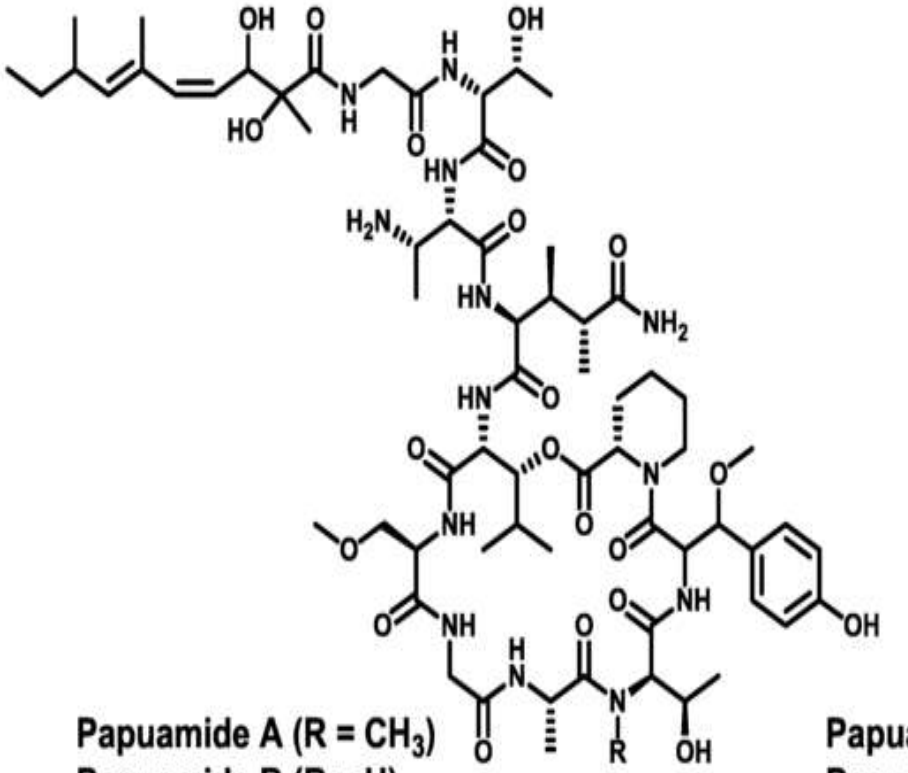
Lamellarin α-20-sulfate



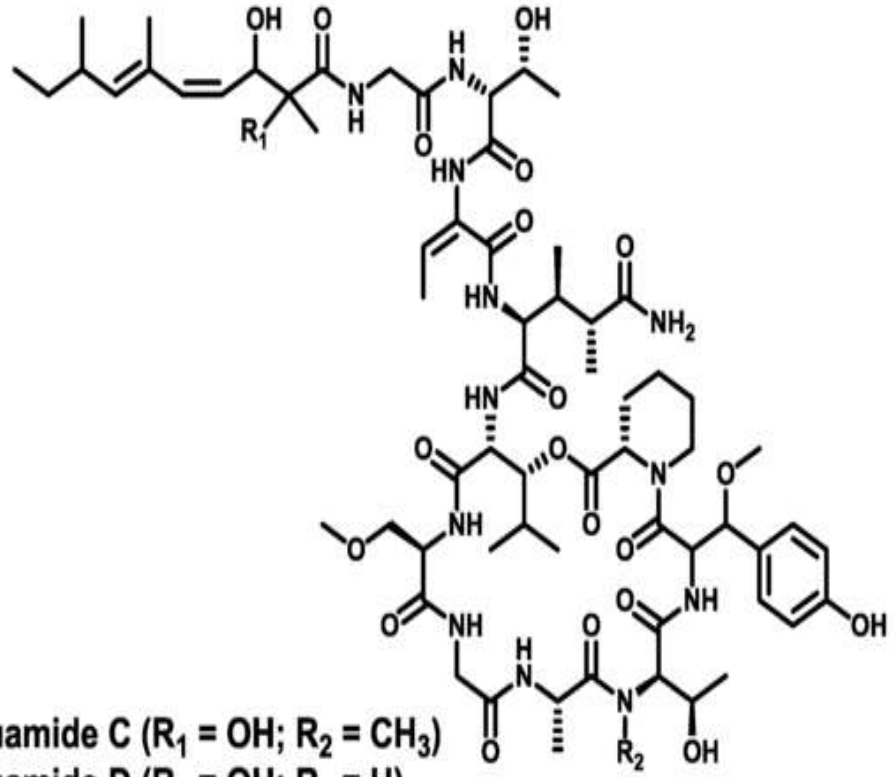
Papuamides A - D

- **Papuamides A, B, C & D were isolated from the sponges *Theonella mirabilis* & *Theonella swinhoei* .**
- **Papuamides A & B inhibited the infection of human T-lymphoblastoid cells by HIV-1 *in vitro* .**

Papuamides A - D



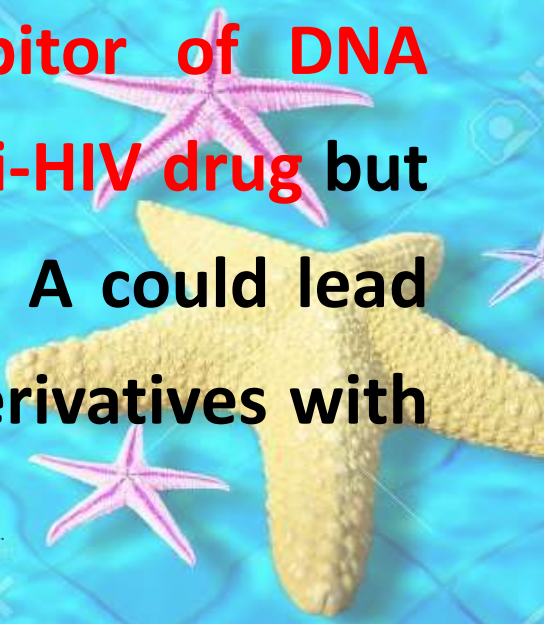
Papuamide A (R = CH_3)
Papuamide B (R = H)



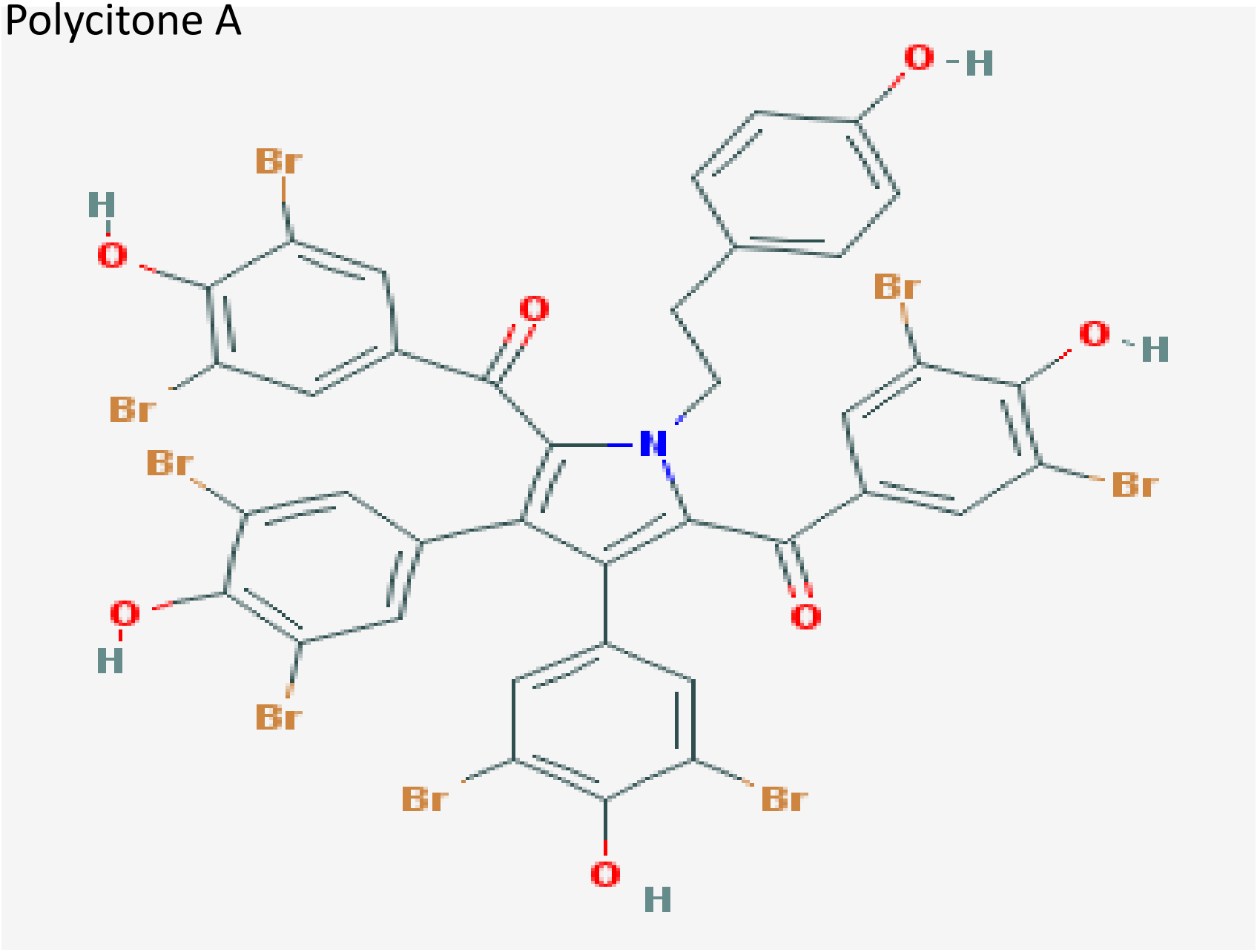
Papuamide C (R_1 = OH; R_2 = CH_3)
Papuamide D (R_1 = OH; R_2 = H)
Papuamide E (R_1 = H; R_2 = CH_3)
Papuamide F (R_1 = H; R_2 = H)

Polycitone A

- **Polycitone A isolated from the ascidian *Polyctor sp.*, is a potent inhibitor of the reverse transcriptase of HIV & both C and B retroviruses, as well as a general inhibitor of cellular DNA polymerases**
- **As polycitone A is a general inhibitor of DNA polymerases it cannot serve as an anti-HIV drug but structural modifications of polycitone A could lead towards the rational design of new derivatives with anti-HIV reverse transcriptase activity**

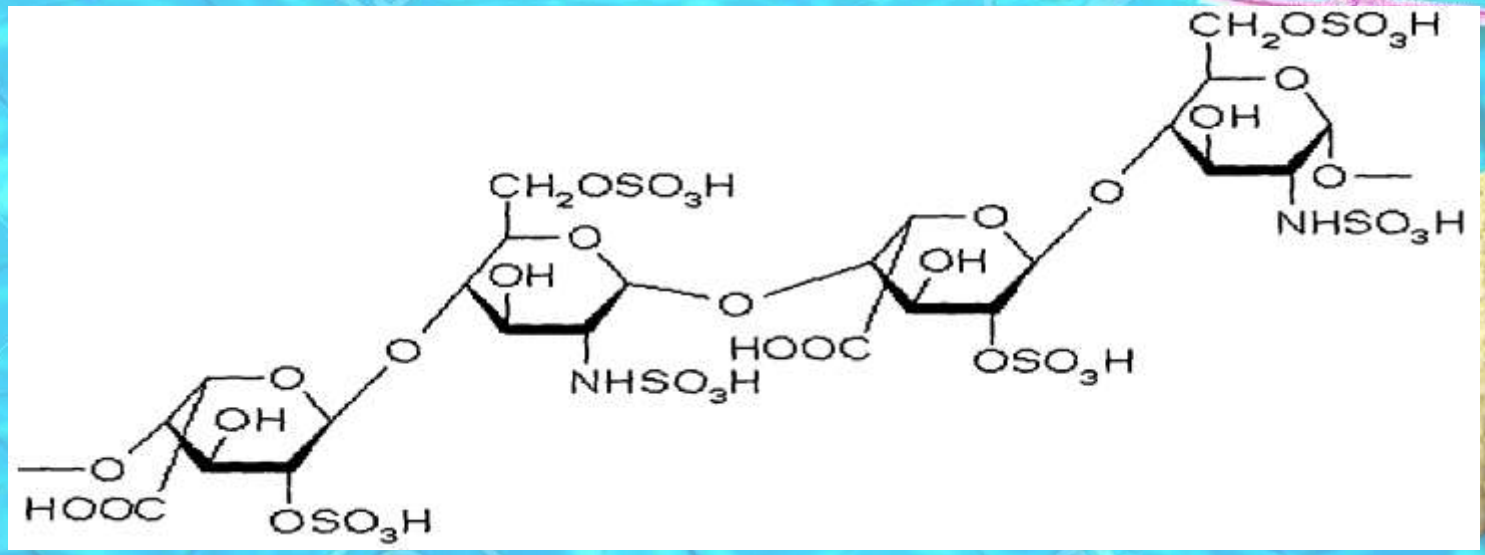


Polycitone A



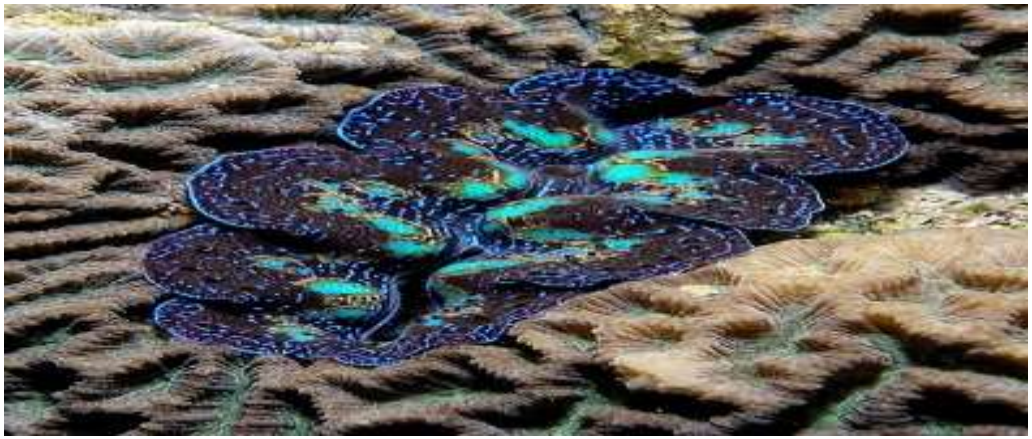
Glucosaminoglycan

- Synthesis of sulfated derivatives of a glycosaminoglycan isolated from the marine bacterium *Pseudomonas sp.* & act against two strains of influenza virus types A & but not B .



Sulfated β-galactan

- Introduction of sulfate groups into polysaccharides containing L-glutamic acid resulted in antiviral activity against influenza virus type A, but not against type B, this activity was similar to that of ribavirin.
- Sulfated β-galactan from the marine clam *Meretrix petechialis* inhibited CD4 HeLa cells from forming syncytia
- It was interpreted as probably the result of a "direct interaction of the polysaccharide with the HIV binding site at the membrane protein receptor CD4".



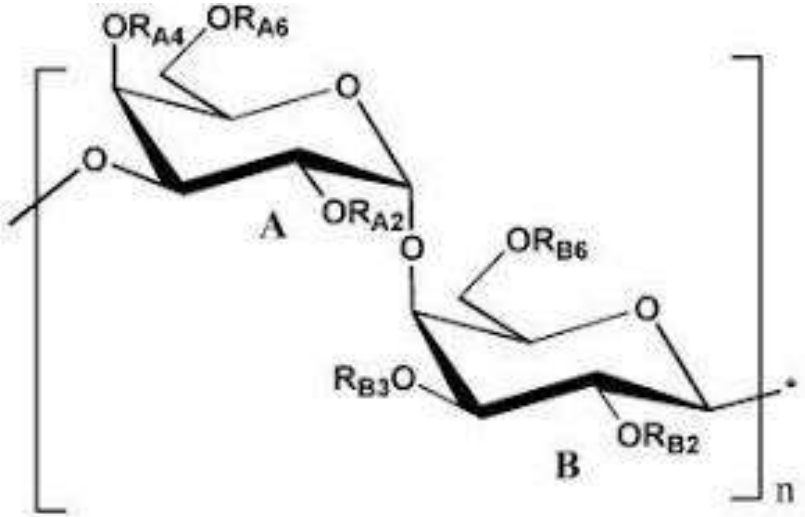


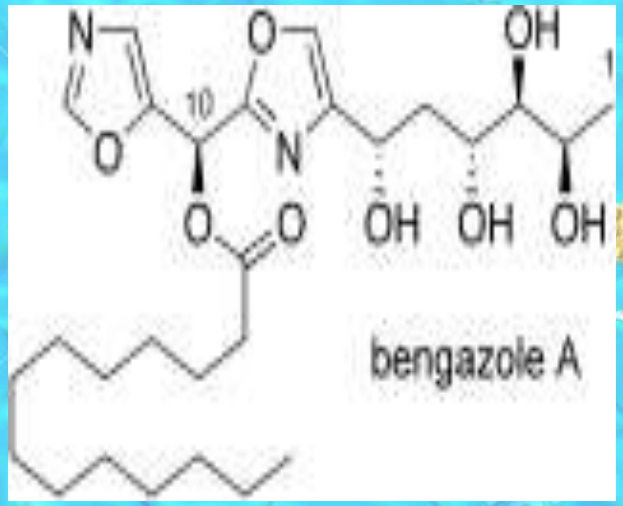
Figure 1 - Schematic and global representation of sulfated galactans from red seaweeds. B unit is in D configuration. R_{A2}: H, SO_3^-; R_{A4}: H, SO_3^-; Pyruvic acid (cyclic ketal with 0_6); R_{A6}: H, CH_3, SO_3^-; Pyruvic acid (cyclic ketal with 0_4), R_{B2}: H, CH_3, SO_3^-; R_{B3}: H, R_{A6}: H, SO_3^-.

Anti-fungals

- Bengazole, bengamide
- Oceanapiside
- Spongistatin I
- Tanikolide
- Theopederins F–J

Bengazole & Bengamide

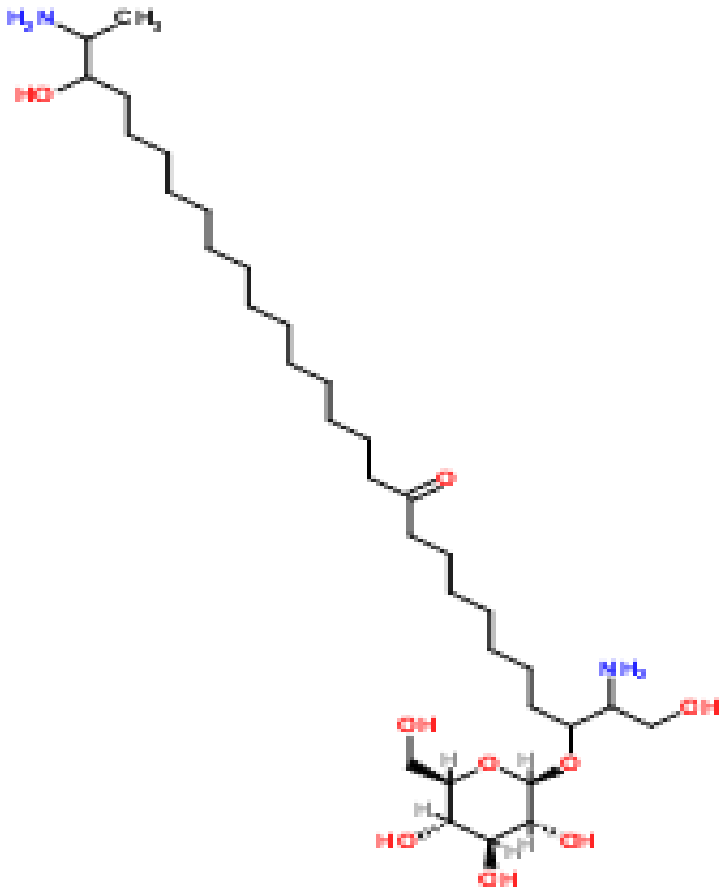
- The bengazole derivatives & a new bengamide obtained from the sponge *Pachastrissa sp .*
- The bengazole derivatives were observed to be active against Candida albicans .



Oceanapiside

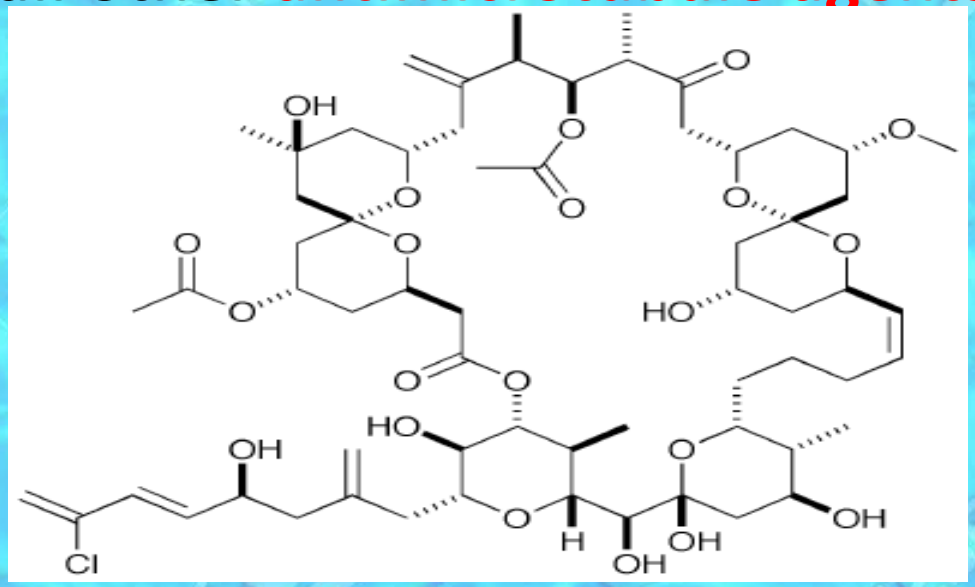
- Oceanapiside, from the sponge *Oceanapia phillipensis*, demonstrated antifungal activity against the fluconazole-resistant yeast *Candida glabrata* .
- Oceanapiside inhibit fungal cell growth by oxidases . ex: Oceanapiside A an inhibitor of sphingolipid biosynthesis.

Oceanapiside



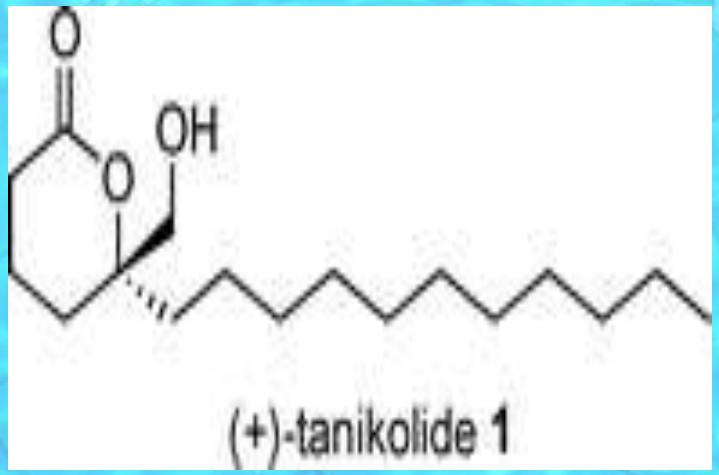
Spongistatin

- **Spongistatin isolated from the sponge *Hyrtios erecta* demonstrated potent microtubule-severing activity**
- **Mechanism of action of was significantly differerent from all other antimicrotubule agents .**



Tanikolide

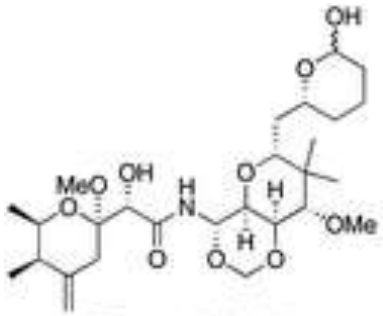
- **Tanikolide was isolated from the marine cyanobacterium *Lyngbia majuscula* .**
- **Tanikolide targets through reverse chemical genetic and proteomic approaches,which has been target based screening for SRIT2 inhibitors .**



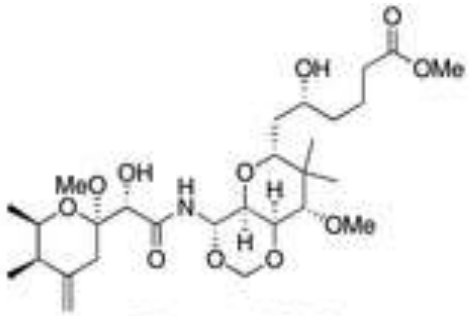
(+)-tanikolide 1

Theopederins F - J

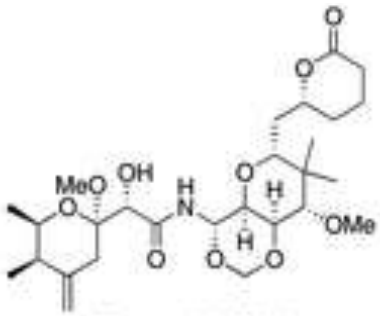
- **Theopederins F–J** ***from the sponge Theonella swinhoei***
- **Theopederin-F was particularly effective against Saccharomyces cerevisiae .**



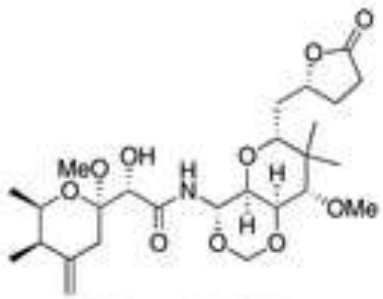
Theopederin A (**6**)



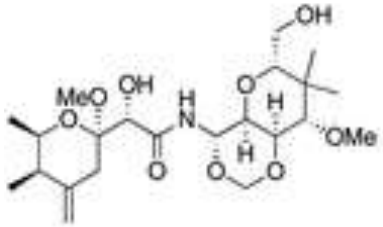
Theopederin B (**7**)



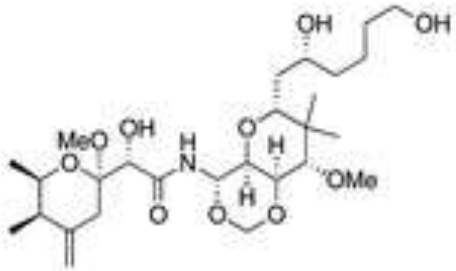
Theopederin C (**8**)



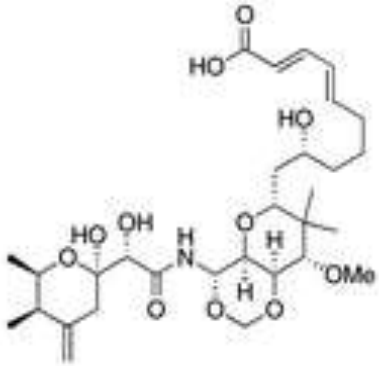
Theopederin D (**9**)



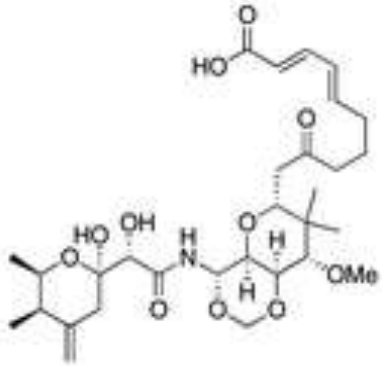
Theopederin E (**10**)



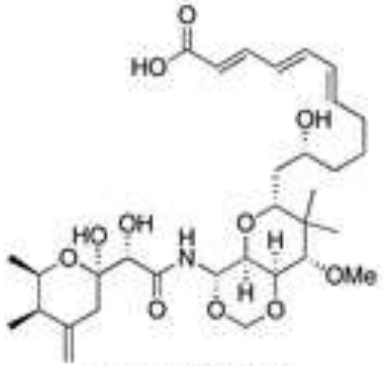
Theopederin F (**11**)



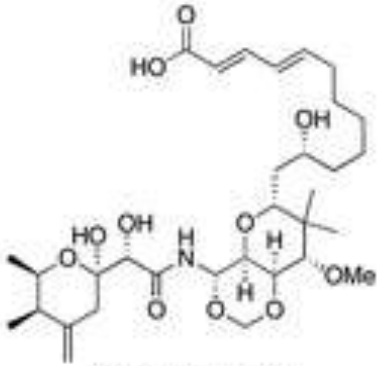
Theopederin G (**12**)



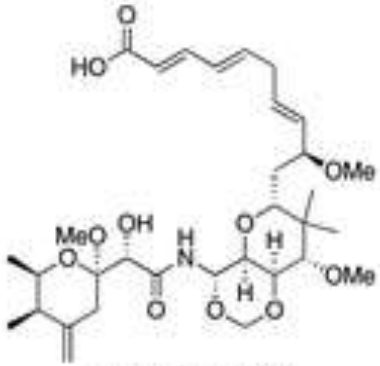
Theopederin H (**13**)



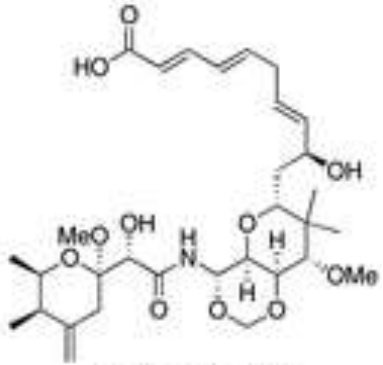
Theopederin I (**14**)



Theopederin J (**15**)



Theopederin K (**16**)

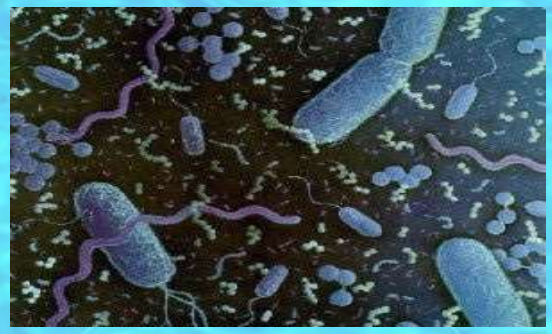


Theopederin L (**17**)

Anti-bacterials

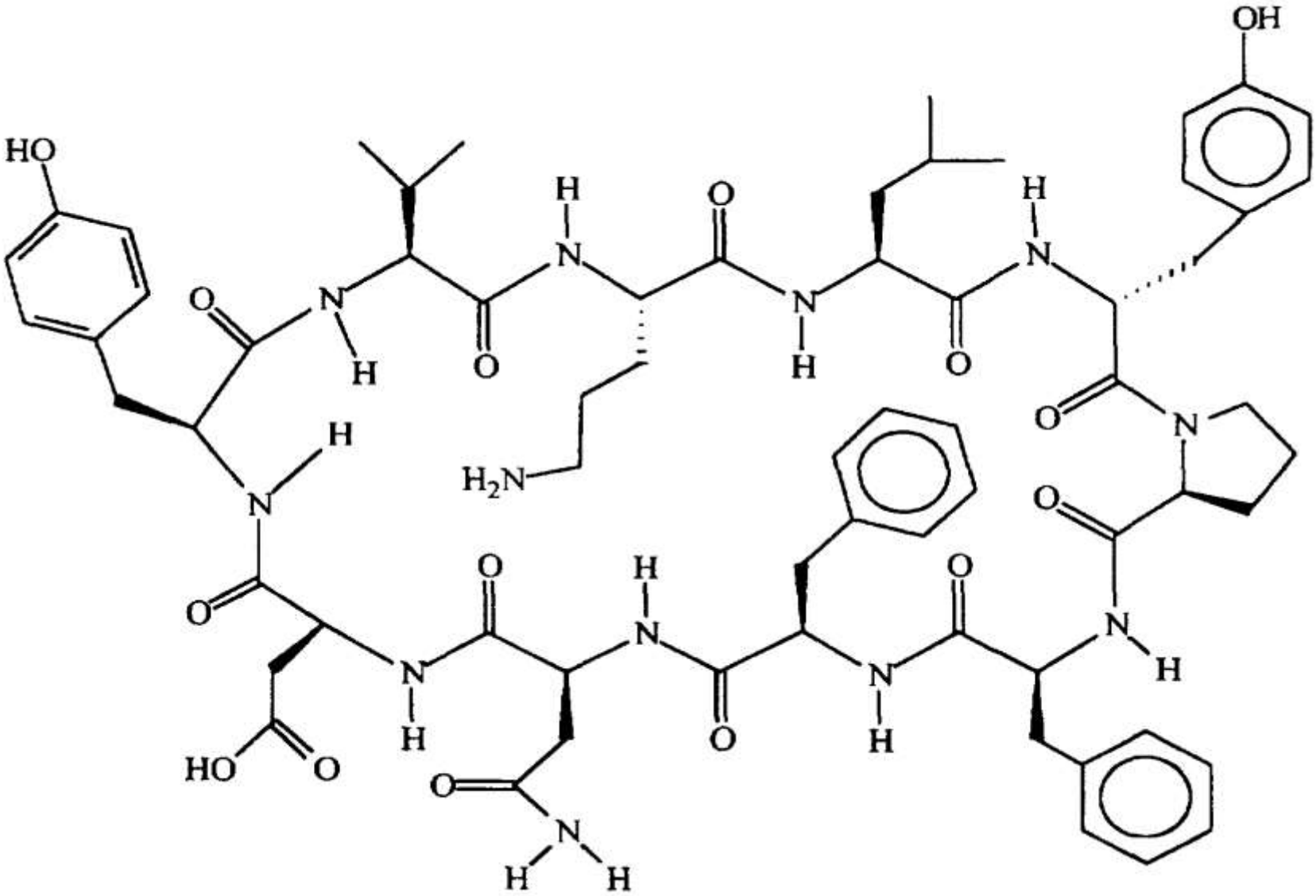
- Loloatins A–D
- Myticin
- Psammaplin A

Loloatins A–D



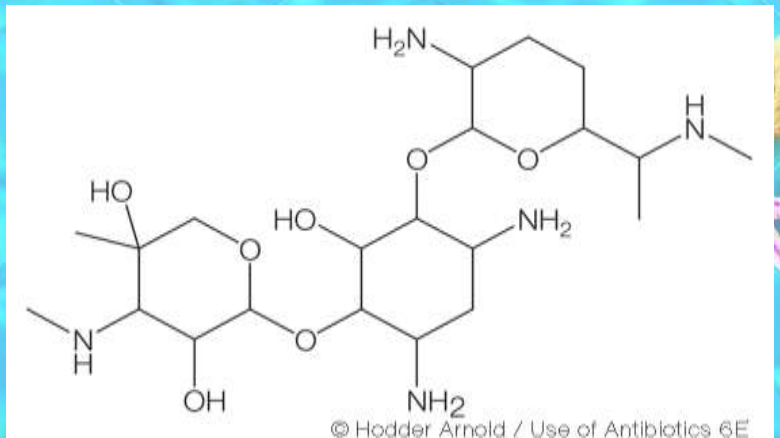
- Cyclic decapeptides isolated from a marine bacterium
- Exhibited *in vitro* antimicrobial activity against methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci & penicillin-resistant Streptococcus pneumoniae.

Loloatin



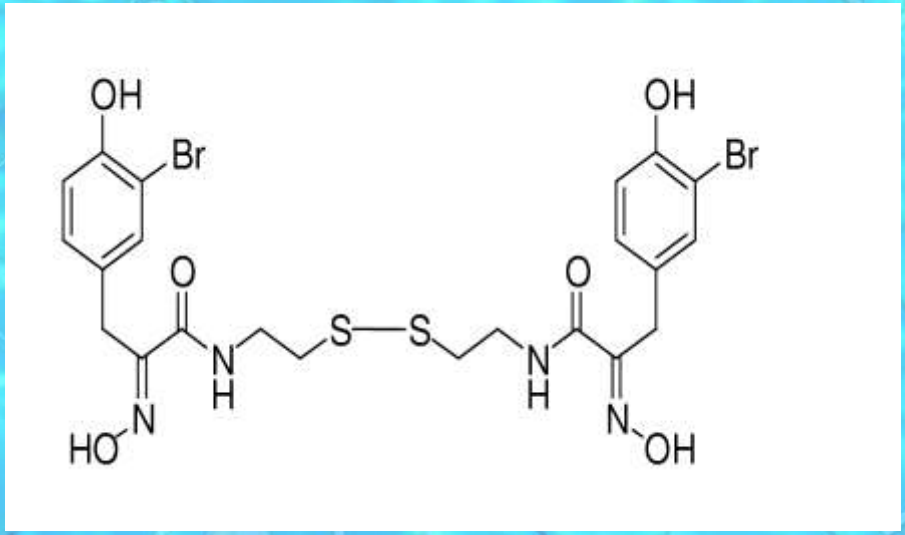
Myticin

- Isolated from hemocytes & plasma of the mussel *Mytilus galloprovincialis*
- Myticins A & B had marked activity against the Gram-positive strains Micrococcus luteus, Bacillus megaterium & Enterococcus viridans, other Gram-positive, Gram-negative bacteria & fungi were unaffected.



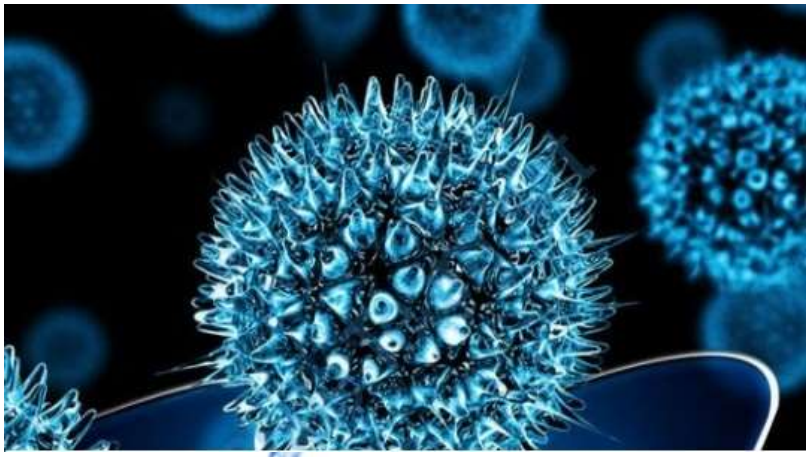
Psammaplin A

- A bromotyrosine derivative from the sponge *Psammaplysilla sp*. possessed antibacterial activity against methicillin-resistant Gram-positive Staphylococcus aureus.



Antiparasitic agents

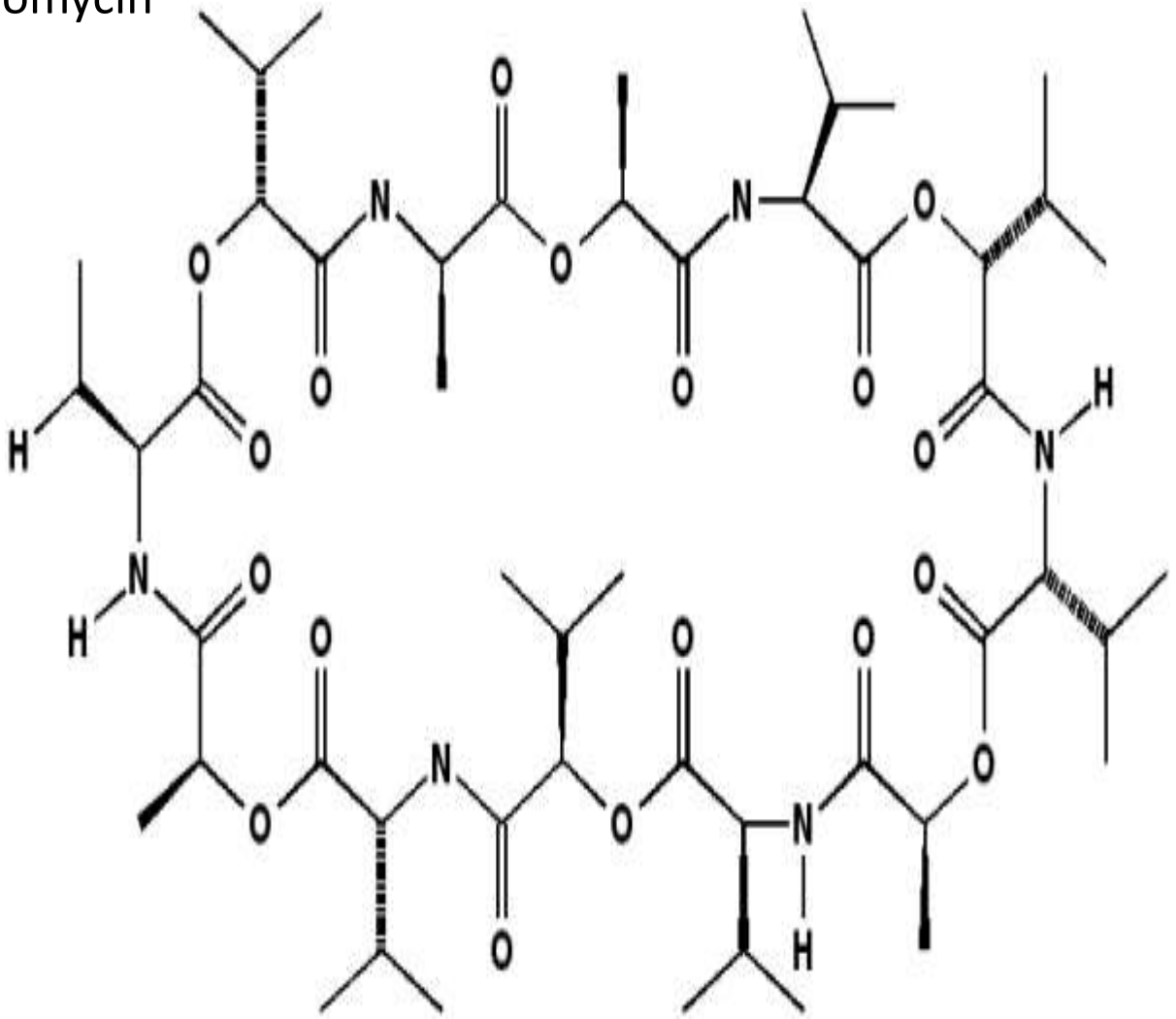
- **Valinomycin**
- **Staurosporine**



Valinomycin

- It was a Dodecadepsi peptide antibiotic .
- It was obtained from the cells of several streptomyces strains , among which *s. tsusimaensis* and *s.fulvissimus.*
- It was recently reported to be the most potent agent against severe acute respiratory syndrome corona virus .

Valinomycin



Starosporine

- It is a natural product originally isolated in 1977 from the bacterium *streptomyces staurosporeus*.
- It was discovered to have bioloical activities ranging from anti fungal to anti hyper tensive .

Cardiovascular compounds

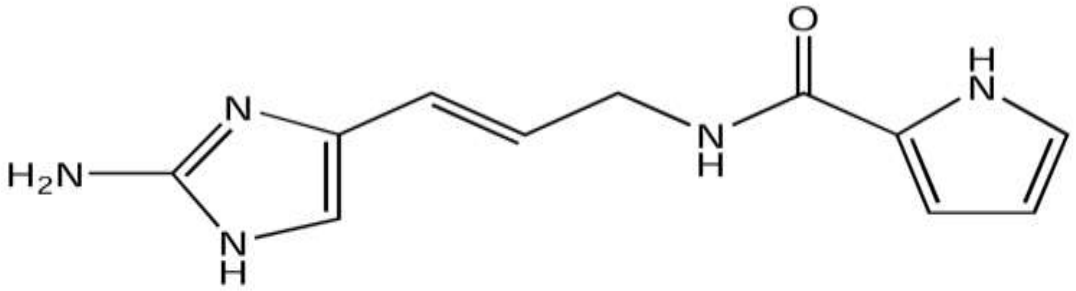
- Anthopleurins.
- Laminine.
- Spongosine

Anthopleurins

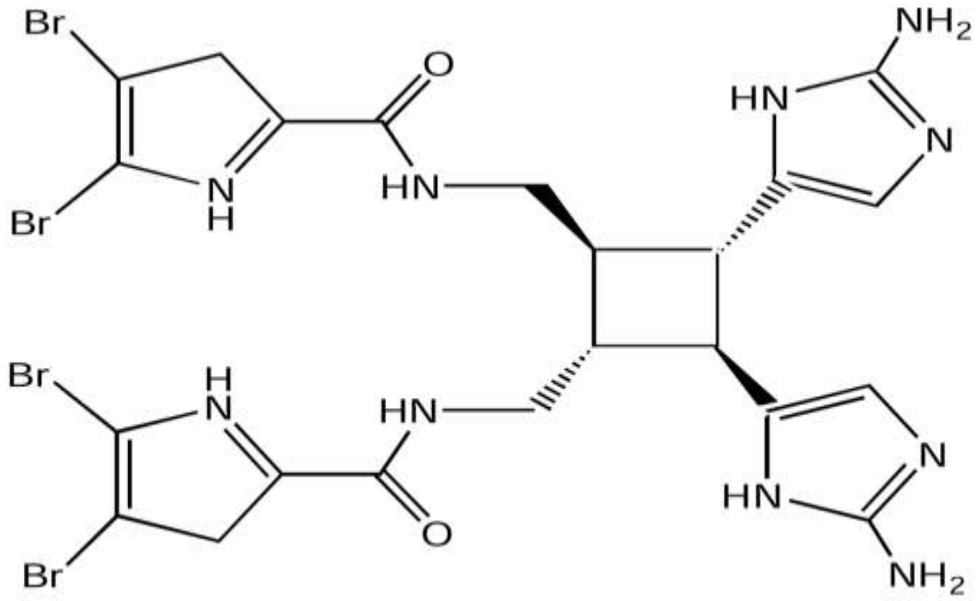
- These are a group of peptides obtaines from “coelenterates”. *Anthopleura xanthogrammica* gives type A & type B .
- *Anthopleura elegantissima* gives type C .
- Anthopleurins AP- A shows strong positive ionotropic action and also produces cardiotonic effect in consious dag.

Anthopleurins

A

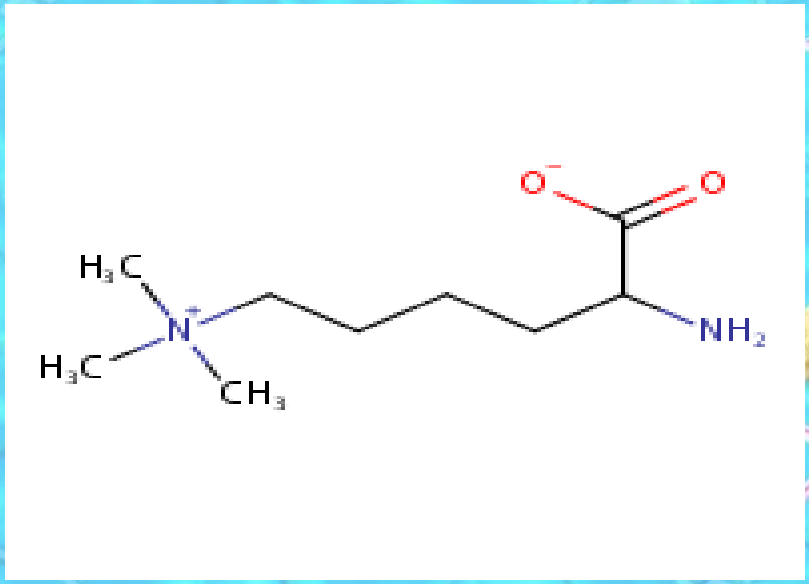


B



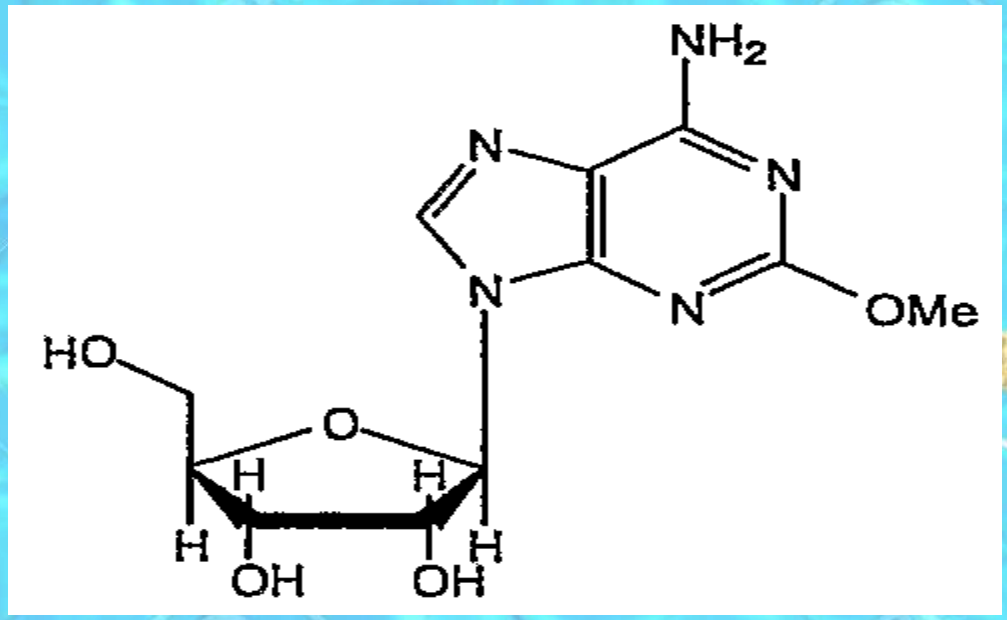
Laminine

- **Laminine is obtained from the marine algae , *Laminaria angustata* .**
- ***Laminaria angustata* gives basic amino acid compound with hypotensive effects .**



Spongosine

- Chemically it is a nucleoside, methoxy derivative of adenosine . It is found in the extract of carrabean sponge *crypotethia crypta* .
- It reduces both the rate & force of contraction of heart.



The available data demonstrates that:

“The marine ecosystem is not only productive to discover novel entities but it is also a tool to identify new cellular targets for therapeutic intervention”

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Thank You....!!!