

## **Recent advances in marine drug research**

Saradavey Vinothkumar and P.S.Parameswaran\*

National Institute of Oceanography Regional Centre,

Dr Salim Ali road

Cochin 682018, India

\* Corresponding author –Dr. P.S.Parameswaran

Tel.: +91 484 2390 814; Fax: +91 484 2390 618.

E-mail address: param@nio.org

### **Abstract**

Structures and properties of promising marine anti-cancer, anti-inflammation and anti-infectious (HIV, HSV, malaria, leishmania) compounds reported during 2008-2011 are discussed. Wherever possible, attempts have also been made to highlight their possible biogenesis or structure-activity relationships (SAR). Since the stress is on identifying and short-listing potential drug molecules, this review is restricted to only those compounds exhibiting promising *in vitro* activity, the arbitrary cut off being  $IC_{50} < 15 \mu M$ , reported during the above period.

### **Keywords**

Anti-cancer, anti-infectious, sponge, anti-inflammation, depsipeptide, lipopeptide, alkaloid.

## Introduction

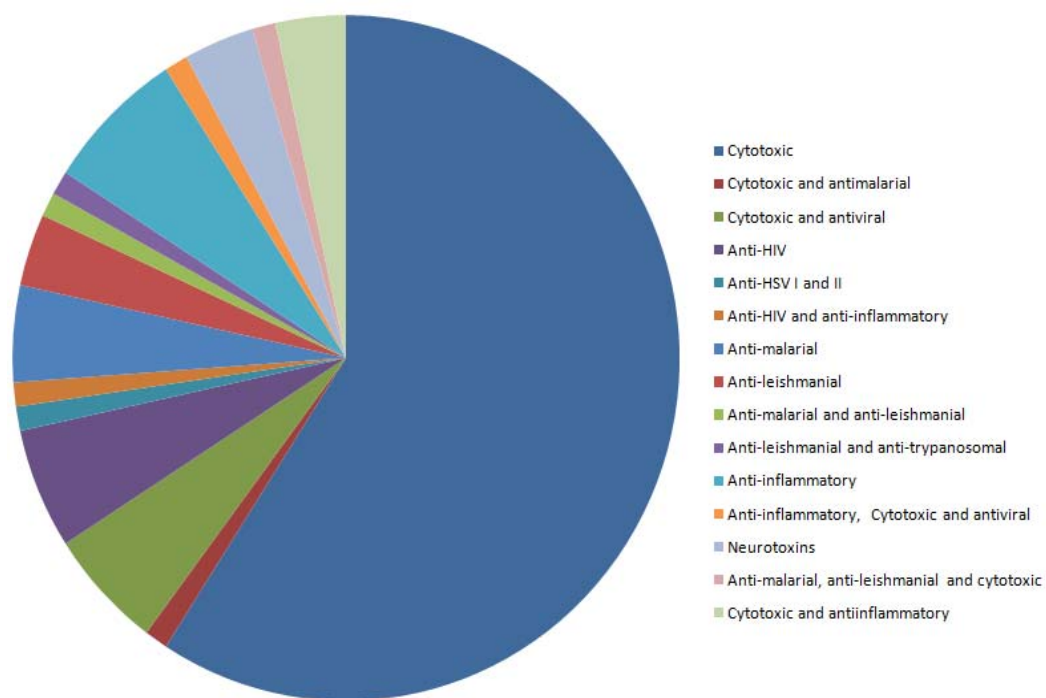
Ocean, covering more than 70% of the Earth's surface is home to nearly one million multicellular (plants and animals) and one billion unicellular (distributed under 100 different phyla) organisms, (Burgess 2012). Living in a highly competitive environment, many of these organisms have perfected the technique of survival through chemical defence. Evolved over millions of years, they are a goldmine of genetic diversity and novel secondary metabolites. Due to several reasons, *viz.*, inaccessibility of their habitats, very low yield of bioactive metabolites, *etc.*, systematic chemical and pharmacological investigations of these organisms were not popular till a few decades ago. However, the recent advances in underwater exploration, natural products chemistry, genome mining and bioassays have led to a great surge in the search for novel biomolecules from this rather underexploited habitat. A cursory review of the literature indicates that more than 70% of marine metabolites are obtained from marine sponges, corals and microorganisms. The contribution from other organisms like molluscs, ascidians and algae adds up to only 30% (Blunt et al. , 2007). The importance of marine metabolites in modern day drug research is revealed by the fact that around 50% of the US FDA approved drugs during 1981-2002 consist of either marine metabolites or their synthetic analogs. Their low effective dosage, better selectivity against target malignant tissues and relative non-vulnerability to resistance development as compared to compounds of terrestrial origin, render them useful target molecules. According to US National Cancer Institute estimates, more than 1% of marine natural products show antitumor properties as against only 0.01% amongst their terrestrial counterparts.

Though serious research in the field of marine pharmacology is of very recent origin, a few products (or their analogues) have already appeared in the market as therapeutic drugs or health food. This includes  $\omega$ -3 poly unsaturated fatty acids (PUFA, cholesterol-lowering), Ara-C (Cytarabine, anticancer), Ara-A (antiviral), ziconotide (analgesic), Trabectedin (anti-cancer) etc. In addition, several more compounds such as bryostatin, didhydrodidemnin, eribulin mesylate, dolastatins, kahalalide F, KRN 7000, squalamine, *etc.*, are at different stages of clinical trials (Mayer et al. , 2010).

The advances in the field of marine metabolites exhibiting diverse biological properties up to early 2008 period have recently been compiled (Mayer et al. , 2011). Subsequently, 3079 new compounds have been added to the literature during the next 4 year period, 2008-2011, (Blunt et al. , 2010, 2011, 2012). As the purpose of this review was to short-list marine compounds of therapeutic potential for common human ailments like cancer, inflammation and infectious diseases, only

compounds having  $IC_{50}$  values  $< 15 \mu M$  are included here. Thus, this review lists 136 cytotoxic, 31 anti-infectious and 24 anti-inflammatory compounds reported during the years 2008-'11 (Fig 1). But for a handful of compounds, which displayed activity at concentrations higher than  $10 \mu M$ , most of these compounds were active at submicro-molar levels. Broadly, these bioactive compounds may be classified into diverse structural types: terpenes, non-terpenes, alkaloids and peptides. The non-terpenoid compounds belong to both acetogenic (C2) and propionate (C3) biosynthetic pathways. Peptides may be either linear or cyclic, including lipopeptides, depsipeptides, etc. Many of these peptides contain L- or D- amino acids,  $\beta$ -amino acids, or other structurally modified amino acids of non-ribosomal origin.

**Fig 1: Classification of compound based on their bioactivity.**



## 1. Marine Sponges

Marine sponges (Phylum: Porifera) constitute one of the most primitive multicellular organisms ( $> 600$  million years old) on earth. Due to their long evolutionary history, these organisms possess vast genetic diversity, producing several novel metabolites of potential biomedical applications. The isolation of sponge-derived antiviral and anticancer nucleosides (spongothymidine and spongouridine) in early 1950's heralded a new era in modern biomedical research. Subsequent

studies over the last six decades have led to the discovery of several novel metabolites, displaying promising biological properties. Herein we report the most active cytotoxic and anti-infectious compounds from 28 sponges reported during the last four years under review. Among these, ten sponges yielded non-nitrogenous compounds (**1-5**, **7-11** and **13-26**), while six animals each yielded alkaloids (**6**, **12**, **27-40**), usual cyclic peptides of 7-9 amino acid residues (**41-51**), or unusual peptides/depsipeptides (**52-68**) (Table 1). Perhaps, the occurrence of novel peptides of possible non ribosomal peptide synthetase (NRPS) or polyketide synthase (PKS) biogenesis indicates their probable microbial origin.

Gukulenins A (**1**) and B (**2**) are tetraterpenoid bis-tropolone derivatives, isolated from a Korean sponge *Phorbas gukulensis*, active against 4 human cancer cell lines (pharynx, stomach, colon, and renal cancer cell lines) at concentrations below 1.0  $\mu\text{M}$  (Park et al. , 2009). The novel  $\gamma$ -lactone containing sesterterpenoids, aplysinoplides A-C (**3-5**) were reported from the Japanese sponge *Aplysinopsis digitata* (Ueoka et al. , 2008). These sesterterpenoids have close structural similarities with manoalide, the antipsoriatic compound, previously reported from the sponge *Luffariella variabilis* (De Silva and Scheuer 1980). Aplysinoplides A and B were active against P388 mouse leukemia cells at  $\text{IC}_{50}$  of 1  $\mu\text{M}$ . Axisonitrile-3 (**6**), a spiro sesquiterpene nitrile active against HepG2 liver carcinoma cells was reported for the first time as a natural product from a marine sponge *Halichondria* sp (Prawat et al. , 2011).

Pandarosides E-J, the new steroidal glycosides with unique 15-keto-16-ene and *cis* C/D ring geometry were reported from a Caribbean sponge *Pandoras acanthifolium* (Regalado et al. , 2010). These compounds as well as their methyl esters displayed promising antiprotozoal activity against *Trypanosoma brucei rhodesiense* and *Leishmania donovani*. Among these, Pandaroside G (**7**) and its methyl ester (**8**), having unsaturation at C-7, exhibited the highest activity ( $\text{IC}_{50}$  = 0.038  $\mu\text{M}$  and 0.051  $\mu\text{M}$ , respectively). The latter compound was also active against multidrug resistant malarial *Plasmodium falciparum* strain. The authors claim that the unsaturation at C-7 increases the activity whereas presence of exomethylene moiety at C-24 (e.g., Pandaroside J **9**) has no positive influence. Another promising metabolite is leiodermatolide (**10**), a unique anti-mitotic macrolide, from the sponge *Leiodermatium* sp, which induces G2/M cell cycle against a range of human cancer cell lines at nanomolar concentrations (Paterson et al. , 2011). Surprisingly, unlike the common antimitotic agents, epothilones, discodermolide, taxanes and vinca alkaloids, leiodermatolide is inactive against purified tubulin *in vitro*.

Recently, a 44-member dilactone macrolide swinholide J (**10**), epoxide of swinholide A, a known cytotoxic compound, was reported from the Red Sea sponge *Theonella swinhoei* (De Marino et al. , 2011). However, comparison of their cytotoxic properties indicated this compound to be less potent against KB oral carcinoma cell lines ( $IC_{50}=1.2/6$  nM for A/J). Mirabilin (**12**), an unsaturated chondropsin-type 35-membered macrolide lactam bearing a conjugated pentadiene and a tetrasubstituted tetrahydropyran ring of mixed polyketide / polypropionate biogenesis is another promising anti-tumor agent. This compound, isolated from the aqueous extract of a marine lithistida sponge *Siliquariaspongia mirabilis* was active against HCT-116 human colon tumor cell line at low micromolar concentrations. SAR studies indicated that the macrolide lactam ring is essential for the antitumor activity (Plaza et al. , 2008). Unfortunately, this compound is highly unstable, decomposing into inactive metabolites within 3-4 hours of exposure to light. Earlier, MacMillan et al. , 2008 had isolated five 14-membered macrolide glycosides, phorbosides A-E, from an Australian sponge *Phorbos sp.*, among which, phorboside C (**13**) was active against HCT 116 cancer cell lines. Lehaulides F (**14**) and G (**15**) are polyketides from the Tongan sponge *Plakrotis sp.*, moderately active against HL60 human leukemia cell line (Barber et al. , 2011). Other natural analogs (Lehaulides E, H-K), were mostly inactive.

Among the sponge-derived non-terpenoids, gracilioethers A-C (**16-18**), isolated from *Agelas gracilis* were active against the malaria parasite *P. falciparum*. In addition, Gracilioether B displayed antileishmanial activity (68% inhibition at 0.029  $\mu$ M) while gracilioethers B **17** and C **18** were also active against P388 cancer cell lines ( $IC_{50} = 0.1$  nM and 2 nM respectively) (Ueoka et al. , 2009). It is possible that the peroxy tricyclic compound **16** could have been formed from the monocyclic precursor **17** via an oxygen mediated cyclization (Scheme 1). Compounds **17** and **18** differ only in the substitution at C-11 position (11-keto in the former and 11 $\alpha$ -hydroxy in latter). While both these compounds display multiple activities, the former displayed ten times greater antileishmanial activity.

The polyunsaturated linear polyene compounds (-) durynes **19-24**, having characteristic diallylic hydroxyl and terminal acetylene groups and active against HeLa Cells were recently reported from *Petrosia sp.* from South Western Japan Sea (Hitara et al. , 2011). It was observed that, the activity increases many fold with increase in chain length. Interestingly (-) duryne was equipotent to the earlier reported enantiomer (+) duryne. Another *Petrosia sp.* yielded two tetracyclic quinones, neopetrosiquinones A (**25**) and B (**26**), moderately active against DLD1 (colorectal adenocarcinoma) and (PANC1 pancreatic carcinoma) cells (Winder et al. , 2011).

1,5-diazocyclohenicosane (**27**), a cyclic diamine from a Kenyan sponge *Mycale* sp. was moderately active against A549 (lung carcinoma), HT29 (colorectal adenocarcinoma) and MDAMB 231 (breast carcinoma) cell lines. This compound is structurally similar to the known anti-invasive and anti-angiogenic sponge metabolites, motuporamines and halichlorensins (Coello et al. , 2009). A few cytotoxic furanoid derivatives, Penasins A-E (**28-32**), cyclic analogs of 4-hydroxy sphingosines were reported from the sponge *Penares* sp. (Ando et al. , 2010). Penasins C-E with an additional methyl group were active against HeLa cells ( $IC_{50} = 4 \mu M$ ). Bioactive aaptamine analogs **33** and **34** were isolated from the sponge *Aaptos* sp. Compound 33 exhibited weak cytotoxicity against human leukemia cells (Shaari K, 2009).

Monanchocidins A-E (**35-39**) novel pentacyclic guanidine alkaloids isolated from a marine sponge *Monanchora pulchra* was found to be cytotoxic. These compounds inhibited HL-60 human leukemia cells at very low concentrations  $IC_{50} = 110-800$  nM (Makarieva et al. , 2011, Guzii et al., 2010). Psammaphysin H (**40**), a new bromotyrosine alkaloid from a marine sponge *Pseudoceratina* sp. displayed more than 97% antimalarial activity at 0.41  $\mu M$  concentration (Xu et al. , 2011).

Several Caribbean and Pacific Ocean sponges were found to have small cyclic peptides of natural L-amino acids. These peptides usually contain 7-10 amino acids with multiple proline residues. Being cyclic in structure, these peptides have lower polarity and are resistant to enzymatic degradation, thereby increasing their bioavailability. Many of these peptides exhibit cytotoxic properties (Table 1.1). Thus, the Dominican sponge *Eurypon laughlini* provided two cyclic heptapeptides, Rolloamides A (**41**) and B (**42**). The former was active against a panel of histologically diverse cancer cell lines with moderate activity in breast, prostate and ovarian cell lines ( $IC_{50} = 0.4$  to  $5.8 \mu M$ ), while the latter was largely inactive (Williams et al. , 2009). Almost simultaneously Vera et al. , 2009 reported three cyclic heptapeptides, Euryjanicin B-D (**43-45**), weakly active against non-small cell lung carcinoma (NSCLC), melanoma, ovarian and renal cancer cell lines, from another Dominican sponge *Prosuberites laughlini*. Examination of their spectral data confirmed that Rolloamide B and Euryjanicin C are 100% homologous. The only difference was the presence of one *cis* and one *trans* L-proline in the former in place of both *cis* L-prolines in the latter. Since the NMR spectra of these compounds were recorded in MeOH- $d_4$  and  $CDCl_3$  respectively, it is possible that the observed stereoisomerism is perhaps solvent-induced. Another interesting observation was the identical amino acid units present in Rolloamide B (**42**) and Stylopeptide 1 (**46**), from the Pacific sponges *Stylostella* sp. and *Phakellia costata* (Pettit et al. , 1995). Surprisingly, these two peptides have identical amino acids, but only 43% homogeneity! A cyclic decapeptide,

Stylopeptide 2 (**47**), reported from *Stylostella* sp. from New Guinea, displayed mild activity against breast cancer cell lines BT-549 and HS 578T (Brennan et al. , 2008). Among the peptides phakellistatins 15-18 (**48-51**) isolated from the sponge *Phakellia fusca* from South China Sea, only phakellistatins 15 (**48**) and 16 (**49**) displayed mild activity against P388 cancer cell line (Zhang et al. , 2010). Phakellistatin 18 (**51**) and Euryjanicin D (**45**) are 70% homologous (amino acids Pro and Tyr in the former being replaced with Phe and Ser in the latter). The presence of similar peptides in different sponges indicates a possible symbiotic origin of these metabolites.

Yaku'amides A (**52**) and B (**53**) are two novel linear peptides containing several dehydro amino acids and  $\beta$ -hydroxy amino acids. These rare metabolites, isolated from the Japanese sponge *Ceratopsia* sp were active against P388 murine leukemia cells (Ueoka et al. , 2010). Among these, Yaku'amide A (**52**) is reported to display a unique mode of action against a panel of 39 cancer cell lines tested.

The common cyclic depsipeptides or lipopeptides of sponge origin have lipids of mixed biogenesis (acetogenic or propionogenic), homo-proline or serine or multiple amino / amido groups. Several of these metabolites showed promising anti-HIV and cytotoxic properties. Homophymine A (**54**), a new anti-HIV cyclodepsipeptide, was isolated from a Caledonian collection of *Homophymia* sp. A cell-based XTT assay revealed its cytoprotective activity against HIV-1 at nanomolar concentrations (Zampella et al. , 2008). The same group subsequently reported nine cytotoxic homophymines from a polar extract of the sponge. Among these, homophymine D1 (**55**) was active against a wide spectrum of cancer cell lines with moderate selectivity against PC3 (prostate carcinoma) and OV3 (ovarian carcinoma) (Zampella et al. , 2009). However, the fact that compound **56** had no effect on caspase 3 and 7 indicated its toxic nature.

Marine sponges of the Lithistida order (Theonellidae) are an important source of non-ribosomal peptides displaying cytotoxicity and anti-HIV properties. Thus, Araki et al. , 2008 isolated koshikamide B (**56**), a cytotoxic cyclic depsipeptide, from a Japanese sponge *Theonella* sp. This compound was active against both P388 and HCT-116 cell lines at very low concentrations ( $IC_{50} = 0.3$  nM and  $0.005$   $\mu$ M, respectively). Related compounds, koshikamides C-H were subsequently isolated from *T. swinhoei* and *T. Cupola* (Plaza et al. , 2010). Among these, koshikamides C-E are linear peptides while the metabolites B, F and H are cyclic depsipeptides. Koshikamides B and H are structurally similar, but for the replacement of an amino acid valine in the former with isoleucine in the latter. Among these compounds F (**57**) and H (**58**) were active HIV inhibitors ( $IC_{50} = 2.3$  and  $5.5$   $\mu$ m respectively), while others were mostly inactive. Comparison of their biological properties

indicated that the urea moiety linked to Asp within the cyclic part enhances the anti-HIV activity, while the presence of –OH group in the pyrrolidione ring reduces the activity (e.g., koshikamide G **59**).

Two structurally different groups of compounds, Celebeside A-C and theopapuamide B-D were isolated from a marine sponge *Siliquariaspongia mirabilis*. Among these, celebeside A (**60**) and theopapuamide B (**61**) were active against both HIV-1 ( $IC_{50} = 0.002\mu M$  and  $0.001\mu M$  respectively) and HCT 116 cancer cells ( $IC_{50} = 0.009\mu M$  and  $0.005\mu M$  respectively) (Plaza et al. , 2009). The lipid part in celebeside A (**60**) is of mixed biogenesis, while that of theopapuamide B (**61**) is of propionogenic origin. Perthamides C (**62**) and D (**63**), the two cyclic octapeptides from the sponge *T. swinhoei* containing several unusual amino acids, were found to be anti-inflammatory with Perthamide C ( $ED_{50} = 0.317 \mu M$ ) claiming to be 100 times more potent than naproxen ( $ED_{50} = 0.158$  mM), the common NSAID drug in the market now (Festa et al. , 2009). Further mechanistic studies are needed before this promising compound could be developed as a potential anti-inflammatory drug. Subsequently, two more anti-inflammatory cyclic peptides, solomonamides A (**64**) and B were obtained from the polar fraction of this extract (Festa et al. , 2011). Bioassay indicated the former to reduce mouse edema up to 60%, while latter could not be tested due to paucity of sample.

The new depsipeptides, mirabamides E-H (**65-68**) displaying strong anti HIV-1 activity ( $IC_{50} = 121, 62, 68,$  and  $41$  nM, respectively) were isolated from an Australian sponge *Stelletta clavosa*. These compounds are structurally similar to mirabamides A-C (from *Siliquariaspongia mirabilis*), but for the replacement of threonine with its dehydration product, 2-aminobutenoic acid. Interestingly, this has resulted in an almost two-fold increase in activity in mirabamides E-H (**65-68**). Since both the sponges are phylogenetically distinct, it is possible that these compounds are of associated microbial origin (Lu et al. , 2011).

## 2. Marine Cyanobacteria

The prokaryotic cyanobacteria continue to be an important source of structurally diverse, bioactive metabolites. A majority of these metabolites are complex peptides, depsipeptides or lipopeptides, containing unusual amino acids, multiple N-methylations and lipids of mixed biogenesis. These compounds have been isolated from pure cultures as well as from wild collections. Out of the promising 21 organisms studied, 11 species yielded cytotoxic compounds, three mixed cultures yielded neurotoxins, yet another three had antileishmanial and one culture, anti-inflammatory compounds (Table 2). The remaining three cultures displayed a combination of



antimalarial and cytotoxicity, antimalarial and antileishmanial or antitrypanosomal and antileishmanial properties.

Most of the anticancer peptides have been reported from predominantly two genera: *Lynngbya* and *Leptolyngbya* sp. Bisebromoamide (**69**) is a novel terminal-protected, linear heptapeptide consisting of D-amino acids, N-methyl amino acids and modified amino acids, obtained from the Okinawan strain of *Lynngbya* sp. This compound was active against a panel of 39 human cancer cell lines and HeLa S3 cells with a mean  $IC_{50}$  of 40nM (Teruya et al. , 2009). It was found that bisebromoamide (**69**) selectively inhibits the phosphorylation of ERK (extracellular signal regulated protein kinase). Aberrant activation of Ras/Raf/MEK/ERK pathway is commonly observed in various cancers. Small molecules targeting these pathways are much sought after in cancer treatment and bisebromoamide could be a lead molecule for this type of therapy in future. Recently, synthesis of bisebromoamide has also been accomplished (Li et al. , 2011).

A Fijian collection of *L. majuscula* yielded desmethoxymajusculamide C (**70**), a cyclic peptide of both L- and D-amino acids, partial N-methylations and an unusual  $\gamma$ -amino acid, together with its open chain analogue. Both the cyclic as well as acyclic metabolites were active against HCT-116 cell line at very low nanomolar concentrations ( $IC_{50}$  = 20 and 16 nM respectively) (Simmons et al. , 2009). Even at low dosage of 52 nM, these compounds caused complete disruption of actin filaments and induced dramatic changes to the cell morphology. Another collection of *L. majuscula* from Singapore afforded the cyclodepsipeptides, hantupeptins A–C, of hybrid polyketide–peptide origin (Tripathi et al. , 2009, 2010 a). Among these, hantupeptin A (**71**) was active against MOLT 4 leukemia cell lines at nanomolar levels ( $IC_{50}$  = 32 nM). Lagunamide A (**72**) and B (**73**), new cyclodepsipeptides from *L. majuscula*, collected from Pulau Hantu Besar, Singapore, was active against P388 murine leukemia cell lines ( $IC_{50}$  = 6.4 and 20.5 nM, respectively). In addition, these compounds also exhibited moderate antiplasmodium and antismearing properties (Tripathi et al. , 2010 b). Lagunamides A (**72**) has comparable anti-malarial activity as dolastatin-15, though it is lower than dolastatin-10, the most potent antimalarial agent of cyanobacterial origin known today. Subsequently, a related compound, lagunamide C (**74**), active against a range of cancer cells ( $IC_{50}$  = 2.1 - 24.4 nM) was isolated by the same group (Tripathi et al. , 2011). A Caribbean collection of *L. majuscula* yielded two new cytotoxic cyclodepsipeptides, itralamides A (**75**) and B (**76**). Among these, itralamide B (**76**) exhibited an order of activity higher than the former, besides also being moderately active against HEK293 human embryonic kidney cells ( $IC_{50}$  = 6  $\mu$ M). It is surprising that

despite close structural similarities the activity of itralamide A (**75**) is much lower than the latter (Jimenez et al. , 2009).

Grassypeptolide A (**77**) a bis-thiazoline containing cytotoxic cyclic depsipeptide ( $IC_{50} = 1.0-4.2 \mu M$ ) has been isolated from extracts of *L. confervoides* (Kwan et al. , 2008). Besides, this molecule also contains a rare  $\beta$ -aminoacid (2-methyl, 3-aminobutyric acid), large number of D-amino acids and several N-methylations. Later, two more related compounds, grassypeptolides B and C (**78-79**) were isolated from the same strain. Among these, Grassypeptolide C (**79**) showed potent antiproliferative activity against HeLa and HT 29 cells ( $IC_{50} = 0.04$  and  $0.07 \mu M$  respectively). Comparison of their cytotoxic properties indicated grassypeptolide C (**79**) to be 16-23 and 65 times more active than grassypeptolides A (**77**) and B (**78**) respectively. Grassypeptolides A and C were found to arrest cell cycle at G2/M stage (Kwan et al. , 2010). SAR studies attribute the increased activity of grassypeptolide C to the R stereochemistry at C-29. Recently, two related metabolites, grassypeptolides D (**80**) and E (**81**) displaying somewhat reduced cytotoxicity against HeLa cells ( $IC_{50} = 335$  nM and  $192$  nM respectively) have been reported (Thornburg et al. , 2011). Almost simultaneously, two more closely related, but lesser active peptides, grassypeptolides F (**82**) and G (**83**), formed by replacement of Thr and N-Me Leu with Val and N-Me Phe were reported from another collection of *L. majuscula* (Popplewell et al. , 2011).

Dragonamide E (**84**), a linear peptide from a Panamanian collection of *L. majuscula* exhibited antileishmanial activity (Balunas et al. , 2010). Another Panamanian collection of the same *L. majuscula* yielded three highly N-methylated linear lipopeptides, almiramides A-C (**85-87**). Among these, almiramides B (**86**) and C (**87**) displayed strong antiparasitic activity against *L. donovani* ( $IC_{50} = 2.4$  and  $1.9 \mu M$ , respectively), whereas compound A (**85**) was inactive up to  $13.5 \mu M$ , indicating the requirement of an unsaturated terminus in the side chain for the activity (Sanchez et al. , 2010). A Panamanian collection of *Schizothrix* sp. yielded a linear peptide gallinamide A (**88**) with unusual 4-(S)-amino-2-(E)-pentenoic acid and methylmethoxy-pyrrolinone at C-terminus. Gallinamide A was moderately active against the malarial strain *L. donovani* and W2 chloroquine-resistant *P. Falciparum* (Linnington et al. , 2009).

Alotamide A (**89**), a novel neurotoxic cyclic depsipeptide featuring three contiguous peptide residues linked to a polyunsaturated dihydroxy lipid moiety was isolated from a marine cyanobacterium *L. bouillonii* during a bioassay-guided screening program (Soria-Mercado et al. , 2009). A lariat-type cyclic depsipeptide, Coibamide A (**90**), active at nanomolar levels against majority of NCI's panel of 60 cancer cell lines was reported from a *Leptolyngbya* strain from

Panama (Medina et al. , 2008). It is proposed that perhaps this compound is acting in a novel way and efforts are on to synthesize the molecule in lab. Another macrocyclic compound of potential biomedical use is Palmyrolide A (**91**), isolated from a mixed cyanobacterial assemblage of *Leptolyngbya cf.* and *Oscillatoria* sp. This macrocyclic lipophilic compound effectively blocks sodium channel (Pereira et al. , 2010). A family of cyclodepsipeptides, veraguamides A-C and H-L, were isolated from a collection of *Oscillatoria margaritifera*. Veraguamides are reminiscent of other cyanobacterial products hantupeptin (**71**) discussed earlier. Veraguamide A (**92**) was highly toxic to H-460 human lung cancer cell line ( $LD_{50} = 141$  nM) (Mevers et al. , 2011). Concurrently, Salvador et al. , 2011 had also isolated veraguamides A-G from a dolastatin-16 producing *Symploca cf. hydnoides* from Guam. Among these, veraguamides D (**93**) and E (**94**) were active against both HT 29 and HeLa cell lines ( $IC_{50} = 0.5-1.5$   $\mu$ M). It is possible that the increased hydrophobicity of specific units in these compounds might be rendering them more active. Viridamides A (**95**) and B (**96**), two new depsipeptides of PKS-NRPS biosynthetic origin were isolated from the marine cyanobacterium *Oscillatoria nigro-viridis* (Simmons et al. , 2008). These compounds possessed a novel 5-methoxydec-9-ynoic acid moiety and an unusual proline methyl ester terminus. Among these, only viridamide A (**95**) showed antitrypanosomal and antileishmanial activities ( $IC_{50} = 1.1$   $\mu$ M and  $1.5$   $\mu$ M respectively), while the other compounds were inactive. This is an example where a subtle change of a methyl into ethyl group in a side chain influences the activity profoundly.

Hoiamides A-C, novel cyclic depsipeptides were reported from several mixed collections of *Symploca* and *Oscillatoria* from Papua New Guinea (Choi et al. , 2010, Pereira A, 2009). Detailed investigations revealed that only Hoiamides A (**97**) and B (**98**) stimulate sodium influx ( $EC_{50} = 1.7$  and  $3.9$   $\mu$ M respectively) and suppress spontaneous calcium oscillations ( $EC_{50} = 45.6$  and  $79.8$  nM, respectively) in mouse neocortical neurons. Largazole (**99**), a modified amino acids-polyketide hybrid from a *Symploca* sp. was active against several cancer cell lines at nanomolar concentrations and displayed remarkable dose-dependent selectivity for transformed cancer cells as against non-transformed cells (Taori et al. , 2008). Further biological studies using synthetic sample revealed that Largazole (**99**) is a potent histone deacetylase (HDAC) class I inhibitor (Bowers et al. , 2008, Ying et al. , 2008). SAR studies revealed that the thiol moiety in Largazole (**99**) is crucial for the activity. Subsequently, a synthetic analogue having a pyridine unit had showed enhanced potency against HDAC enzymes (Bowers et al. , 2009). Symplocamide A (**100**), active against NCI-H460 non small lung cancer cells and neuro-2A mouse neuroblastoma cells ( $IC_{50} = 40$  &  $29$  nM respectively), from *Symploca* sp. found in Papua New Guinea is yet another promising drug lead (Linington et al. , 2008). Besides, this compound also showed weak anti-malarial and anti-leishmanial properties.

Structure of symploramide A (**100**) was similar to other serine protease inhibitors with an additional citrulline moiety at P1 position, crucial for protease binding. Evaluation of its biological properties revealed a 200 fold enhanced inhibition of chymotrypsin over trypsin, a desired property for any anticancer drug molecule. Minutissamides A-D, are multiple N-methylated cyclic decapeptides containing unusual amino acids and  $\beta$ -amino acids, isolated from the cultured cyanobacterium *Anabaena minutissima*. All the four compounds have identical peptide cores and differ only in the lipophilic  $\beta$ -amino acid residue. Among these, the least polar compound Minutissamide A (**101**), having 2-hydroxy-3-amino-4-methyl dodecanoic acid as the beta amino acid constituent exhibited highest activity against HT-29 cancer cell line. Conversion of the terminal methyl into chloromethyl or further chain extension with polar, oxygen-containing groups reduces the activity (Kang et al. , 2011).

Compared to peptides and depsipeptides, the cytotoxic properties of linear cyclic macrolides of cyanobacterial origin are not very promising. One moderately active metabolite is caylobolide B (**102**), isolated from *Phormidium* sp. from Florida and active against HT 29 and HeLa cancer cells (Salvador et al. , 2010). This compound is an analogue of the known cytotoxic, cyanobacterial metabolite, Caylobolide A (MacMillan and Molinski 2002). Another non-peptide molecule of cyanobacterial origin, which is also a good nitric oxide inhibitor, is malyngamide F acetate (**103**), from *L. majuscula*. Mechanistic studies indicate that this compound acts through a novel MyD88 (Myeloid differentiation primary response gene 88) dependent pathway of inflammation, raising the possibility of its emerging as an effective drug (Villa et al. , 2010). Another closely related anti-inflammatory compound is malyngamide 2 (**104**), isolated from *L. sordida* (Malloy et al. , 2011).

### 3. Marine Actinomycetes

Marine actinomycetes continue to be a good source for novel bioactive compounds (esp. antitumor, antimalarial and antimicrobial agents) of mixed biogenesis (Table 3). Their novel structures, promising biological properties and prospects of fermentation-based mass production have led to a renewed interest in the search for potential drugs from this group of marine microorganisms. Herein we report the novel cytotoxic compounds isolated from this promising group of microorganisms during the last four years. These compounds belong to diverse structure types: pyrones (**105-110**), macrolides or polypropionates (**111-114**), alkaloids (**115-122**), peptides (**123-125**) and glycoside (**126-129**).

Marinactinones A-C (**105-107**), the new  $\gamma$ -pyrones, exhibiting weak cytotoxic properties were isolated from *Marinactinospora thermotolerans*, a novel genus of marine actinomycetes (Wang et al. , 2011). Out of these, compounds **105** and **107** exhibited moderate cytotoxicity against SW1990 (pancreatic adenocarcinoma), HepG2 and SMCC-7721 (hepatic carcinoma) cell lines. In addition, the former compound was also found to be a weak inhibitor of DNA topoisomerase II. The anthraquinone- $\gamma$ -pyrones, saliniquinones A-F, isolated from the actinomycete *Salinispora arenicola* closely resemble the well known antibiotic and anticancer agents, pluramycins but for the presence of differently functionalized linear C5 side chains at C-2. It is well established that the antitumor properties of pluramycins arise from their ability to alkylate N<sub>7</sub> residues of guanine base in DNA by intercalation. Among different analogs, saliniquinone A (**108**), which had an epoxide and a terminal unsaturation was active against HCT116 cells at nanomolar concentration (Murphy et al. , 2010). Comparison of the antitumor properties of different analogs confirmed that opening of epoxide and saturation of the terminal double bond reduces the activity. Four  $\alpha$ -methoxy- $\gamma$ -pyrones containing highly substituted tetraene side chains were isolated from *Streptomyces albus*, of which the compounds (**109**) and (**110**) were active against breast, lung and colon cancer (Schleissner et al. , 2011).

Another interesting group of compounds are indoxamycins A-F, the novel tricyclic polypropionates from the marine actinomycete strain NPS 643. Among these, indoxamycins A (**111**) and F (**112**) caused significant growth inhibition of HT29 cells. The lesser active indoxamycins B-E are oxidation products of Indoxamycin A (Sato et al. , 2009). Tartrolon D (**113**) isolated from a *Streptomyces* sp. along with the known metabolite, Ikarugamycin was found to be moderately active against A549, HT29, and MDA-MB-231 cancer cell lines (Perez et al. , 2009). A new metabolite cryptosphaerolide (**114**), an eremophilane-type sesquiterpenoid skeleton esterified to a C11 acid of propionate origin, active against HCT-116 cell lines, was isolated during saline fermentation of the marine-derived ascomycete fungal strain CNL-523 (*Cryptosphaeria* sp.). This compound inhibits the protein Mcl-1 (IC<sub>50</sub> = 11.4  $\mu$ M), a member of the Bcl-2 family involved in apoptosis and hence might emerge as an anticancer drug in the near future (Oh et al. , 2010).

Recently, few naturally occurring terpenyl- $\alpha$ -nitropyrroles, Nitropyrrolins A-E, were isolated from the marine actinomycete strain CNQ-509. Out of these, Nitropyrrolin D (**115**) having a tri-unsaturated side chain was moderately active against HCT-116 human colon carcinoma cells (Kwon et al. , 2011). Caerulomycins F-K, are bipyridine alkaloids of possible amino acid-polyketide biosynthetic origin, isolated from *Actinoallotheichus cyanogriseus*. Out of these only caerulomycin I

(**116**) inhibited growth of K562 myelogenous leukemia line cancer cells (Fu et al. , 2011). Two novel spiroaminals, marineosins A (**117**) and B (**118**), containing two pyrrole moieties each, were reported from a marine sediment-derived *Streptomyces* sp. (Boonlarppradab et al. , 2008). The marineosins are structurally related to prodigiosin class of bacterial pigments. Bioassay studies indicated marineosin A (**117**) to be more potent against HCT 116 cancer cells ( $IC_{50} = 0.5 \mu M$ ), probably due to the differences in configuration at the spiral centre and conformational changes around the tetrahydropyran ring. Another actinomycete strain, *Saccharomonospora* sp. yielded a novel alkaloid Lodopyridone (**119**), active against HCT-116 cancer cells (Maloney et al. , 2009). The *Streptomyces* strain CNR-698 from the Bahamas Islands yielded ammosamides A (**120**) and B (**121**), two novel pyrrolo-iminoquinone compounds active against HCT-116 colon carcinoma ( $IC_{50}=320$  nM). These compounds also displayed pronounced selectivity when tested against several cancer cell lines ( $IC_{50} = 1-20$  nM), indicating a specific target mechanism of action. Fluorescent labelling studies helped in identifying myosin and other cellular proteins as the targets of these compounds (Hughes et al. , 2009a, Hughes et al. , 2009b). Several syntheses of these compounds and analogs have recently been reported (Hughes et al. , 2010, Reddy et al. , 2010, Wu et al. , 2010). Mansouramycin C (**122**), yet another promising alkaloid from the marine *Streptomyces* strain Mei37 was found to be selectively active against 10 out of 36 cancer cell lines tested (mean  $IC_{50} = 0.089 \mu M$ ), (Hawas et al. , 2009).

Three new cyclohexadepsipeptides arenamides A-C (**123-125**) were isolated from the marine actinomycete *Salinispora arenicola*. Out of these, the former two compounds, having an aromatic amino acid Phenyl alanine in the molecule, inhibited NO production in a dose dependent manner (2-10  $\mu M$ ), besides displaying weak activity against HCT116 cells (Asolkar et al. , 2009). In contrast, compound **125**, where above amino acid residue has been replaced with methionine, was found to be totally inactive.

Lobophorins C (**126**) and D (**127**), two kijanimicin-like macrolides of mixed biogenesis were isolated from a marine sponge (*Hymeniacidon* sp.) harbouring an associated actinomycete strain AZS17. These compounds possess a pentacyclic core linked to 3 units of L-digitoxose and a rare nitro sugar, 2,3,4,6-tetraoxy-4-(methylcarbamyloxy)-3-C-methyl-3-nitro-D-xylo-hexapyranose, commonly known as D-kijanose. Both these compounds were structurally very close but for the substitution of group at C3 position of D-kijanose ( $-NO_2$  in lobophorin C and  $-NH_2$  in Lobophorin D). These compounds showed selective inhibition of cancer cell lines. Thus lobophorin C was active against liver cancer cell line 7402 ( $IC_{50}$  0.5 nM) while lobophorin D was active against breast cancer MDA-MB 435 ( $IC_{50}$  6 nM). These differences in selectivity caused by the presence of  $-NO_2$  or -

NH<sub>2</sub> is intriguing (Wei et al. , 2011). Earlier, two related metabolites, lobophorins A (**128**) and B (**129**), were reported from an unidentified actinomycetal strain associated with a brown alga (Jiang et al. , 1999). Closer examination of these structures revealed lobophorins A (**128**) and B (**129**) to be almost identical to D (**127**) and C (**126**) respectively, but for the *cis/trans* stereochemistries of 28 and 29 methyls (*cis* in C & D, *trans* in A & B). While lobophorins C and D have comparable optical rotation, reported values for A and B vary widely [ $(\alpha)_D = -175^\circ$  and  $+106^\circ$  respectively]. Recently, two more related compounds, lobophorins E (**130**) and F (**131**) were isolated from another strain SCSIO 01127 from South China. The aglycone part of these compounds are similar to lobophorin B (**129**), but for the extra oxygen at C-28. The sugar moieties in lobophorins B & E are identical, while Lobophorin F has one sugar moiety less. Lobophorin F (**131**) is active against SF268 (human glioblastoma), MCF7 (breast cancer) and NCI-H460 cancer cells (IC<sub>50</sub> 2.9-6.8  $\mu$ M), while compound **130**, is inactive (Niu et al. , 2011),.

#### 4. Soft corals (order Alcyonacea, class Anthozoa)

Soft corals are a rich source for bioactive compounds including prostanoids, different sterols and cyclic diterpenoids (Table 4). Thus, claviridins A-D (**132-135**), new cytotoxic prostanoids from a Taiwanese soft coral *Clavularia viridis* were active against HepG2, Daoy, WiDr and HeLa cell lines (Shen et al. , 2010). Chao et al. , 2011 isolated six new withanolides from a Formosan soft coral *Paraminabea acronocephala*, out of which, four metabolites, paraminabeolides A-D (**136-139**) showed mild anti-inflammatory properties. In addition, paraminabeolide A (**136**) was also moderately active against HepG2 cells (IC<sub>50</sub> 8.0  $\mu$ M).

Among the assorted diterpenoids of soft coral origin, gyrosanols A (**140**) and B (**141**) from *Simularia gyrosa*, showed antiviral activity against HCMV (human cytomegalovirus) (IC<sub>50</sub> 2.6 and 3.7  $\mu$ M respectively) and anti-inflammatory properties (Cheng et al. , 2010). Two new eunicellin-type diterpenoids, cladielloides A (**142**) and B (**143**) possessing a 2-hydroxybutyroxy group in their structures were isolated from an Indonesian octocoral *Cladiella* sp. Among these, cladielloide B (**143**) exhibited moderate activity against human leukemia CCRF-CEM tumor cells (IC<sub>50</sub> 0.009  $\mu$ M) besides inhibiting superoxide anion generation and elastase release by human neutrophils at 0.02  $\mu$ M (Chen et al. , 2010). It will be interesting to note that another eunicellin derivative (-) 6 $\alpha$ -hydroxy polyanthellin A (**144**) exhibiting promising antifouling properties against barnacle larvae *Balanus amphitrite* (IC<sub>50</sub> 0.023  $\mu$ M) were isolated in our lab from an Indian soft coral *Cladiella krempfi* (Mol et al. , 2011). Out of several eunicellin diterpenoids isolated from *Klyxum simplex*, klysimplexin R (**145**), having the bicycle [4.0.8] skeleton with unsaturations at  $\Delta^{2,6}$  positions exhibited promising

anti-inflammatory activity. The activity was lost when  $\Delta^6$  was epoxidised (e.g., klysimplexin Q). But its pyran derivate klysimplexin S (**146**), obtained by oxygenation of both the double bonds followed by additional limited oxygenations and esterifications (mainly in ring B) is equally active. The remaining more oxygenated metabolites, having multiple acetates in ring A were all inactive (Chen et al. , 2011). Out of three xenicane diterpenoids, asterolaurins K-M, isolated from *Asterospicularia laurae*, asterolaurin L (**147**) was active against the HEP-2 , Daoy, MCF-7 and WiDr tumor cell lines, while the other two metabolites were inactive (Lin et al. , 2011b). The observed cytotoxicity of asterolaurin L (**147**) is perhaps due to the presence of epoxide at C7-C8 and hydroxyl group at C-15. The inactive asterolaurin K has unsaturation between C7-C8 and OMe group at C15.

Cembranolides, the dominant diterpenes found in *Sinularia*, *Sarcophyton* and *Lobophytum* genera are characterized by a 14-membered carbocyclic nucleus, sometimes fused to five-, six-, or seven-membered lactone rings. Many of these compounds display anti-inflammatory and/or cytotoxic properties. The Chinese soft coral *S. flexibilis* yielded Sinulaflexiolides A-F, out of which, sinulaflexiolides D (**148**) and E (**149**) were selectively active against the gastric gland carcinoma cell line (BGC-823). Comparison of structure-activity relationships indicated that methyl or ethyl esters show greater activity than 6- or 7-membered lactones (Wen et al. , 2008). Crassarines F (**150**) and H (**151**), structurally dissimilar metabolites of cembrane skeleton from *S. crassa* significantly reduced the expression of pro-inflammatory proteins iNOS ( $35.8 \pm 10.7\%$ ) and COX-2 ( $65.6 \pm 6.2\%$ ) at 10  $\mu\text{M}$  level concentrations (Lin et al. , 2010). Bioassay-guided purification of the extract of *Sarcophyton crassocaule* yielded sarcocrassocolide I (**152**) as the most potent cytotoxic agent from a mixture of 7 similar compounds, all exhibiting varying degrees of cytotoxic and anti-inflammatory properties (Lin et al. , 2011a).

Ahmed et al. , 2008 had earlier reported gibberosene A (**153**), a close structural analog of compound **150**, capable of reducing iNOS ( $76.2 \pm 6.7\%$ ) and COX-2 proteins ( $54.0 \pm 6.2\%$ ) in LPS stimulated cells from the soft coral *S. gibberosa*. Compound **153** is also a monohydroxy cembrane derivative like **150**, the only change being in the shifting of OH group from C-9 to C-14. Chao et al. , 2008 identified six new cembranolides, crassumolides A-F from *Lobophytum crassum*, out of which crassumolides A (**154**) and C (**155**) were found to inhibit iNOS and COX-2 expression in RAW 264.7 macrophages ( $\text{IC}_{50} < 10 \mu\text{M}$ ), besides being active against Ca 9-22 oral cancer cells. Subsequently, three more related compounds, crassumolides G-I, displaying similar properties were identified from this organism (Tseng et al. , 2011). Cheng et al. , 2008 reported durumolides A-C (**156-158**), which inhibited both the iNOS and COX-2 proteins in LPS-activated RAW 264.7 cells *in*



*vitro* ( $IC_{50} < 10 \mu M$ ), from a related soft coral *L. duru*. Subsequently, they also reported a few more structurally similar anti-inflammatory metabolites, durumolides D-Q, from the same soft coral (Cheng et al. , 2011, Cheng et al. , 2009). Compounds **154-158** have  $\alpha$ -methylene- $\gamma$ -lactone moieties fused to the normal cembrane skeleton, a structural feature crucial for the observed anti-inflammatory properties. Recently, Kao et al. , 2011 has reported five novel  $\alpha$ -chloromethylhydroxy- $\gamma$ -lactones, lobocrassin A-E, from the South China soft coral, *L. crassum*, out of which, lobocrassin B (**159**), exhibited modest activity against MOLT-4 and CCRF-CEM cells ( $IC_{50} = 0.34$  and  $0.48 \mu M$  respectively). This compound also displayed anti-inflammatory activity through suppression of the superoxide anion generation and release of elastase by human neutrophils.

## 5. Miscellaneous

The marine brown alga *Dictyota pfaffii* yielded a bicyclic diterpene, dolabelladienetriol (**160**) which inhibited HIV reverse transcriptase enzyme ( $K_i=7.2 \mu M$ ), indicating its potential use for anti-HIV-1 therapy (Cirne-Santos et al. , 2008). Another promising anti-HIV-1 agent was the polymeric phloroglucinol derivative, 6, 6<sup>1</sup>-bieckol (**161**) isolated from the Korean brown alga *Ecklonia cava*. This compound inhibited HIV-1 reverse transcriptase (RT) enzyme activity during laboratory studies ( $EC_{50} = 1.07 \mu M$ ; Artan et al. , 2008). The Indian red algae *Scinaia hatei* and *Sebdenia polydactyla* yielded an anti-viral sulfated xylomannan (**162**), capable of inhibiting human simian virus HSV-1 and HSV-2 with low cytotoxicity. It was noticed that the antiviral activity of the compound is primarily influenced by the degree of sulfation. The exact mechanism of action is yet to be studied, but is speculated to be via interference with the virus multiplication cycle (Ghosh et al. , 2009, Mandal et al. , 2008).

From the New Zealand ascidian *Didemnum* sp. two new indole spermidine alkaloids, Didemnidines A (**163**) and B (**164**) were isolated. Among these, Didemnidine B as well as one of its synthetic precursors exhibited mild activity against the malaria parasite *P. falciparum* (Finlayson et al. , 2011). Opacaline B (**165**) and C (**166**) are two  $\beta$ -carboline containing metabolites from the New Zealand ascidian *Pseudodistoma opacum*, displaying moderate activity against *P. falciparum* (Chan et al. , 2011).

## 6. Conclusion

Systematic research during the last four years has led to the isolation and identification of several new bioactive compounds of potential therapeutic use. This includes areas of utmost concerns to the humanity, viz., treatment of cancer, viral and protozoan infections, inflammation, etc.

Efforts to include marine organisms based drug discovery programmes for other tropical diseases should be initiated, especially for treatment of multidrug resistant and recurrent infectious diseases. Many promising natural products could not be developed into potential therapeutic agents owing to supply problems.

Efforts are now on to identify the 'real' microbial source of several promising drug molecules and further, to develop suitable fermentation strategies to ensure their continued supply in future. In this context, cyanobacteria, actinomycetes and other marine microorganisms are found to be promising sources for novel therapeutic agents. Genetic studies on heterologous expression of biosynthetic gene clusters in other organisms could also be another viable option. In future, interdisciplinary research, collaborative effects, technical advancements in isolation and cultivation of microorganisms could pave the way for more promising and affordable drugs.

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**Table 1: Sponge metabolites**

<b>Source</b>	<b>Compound</b>	<b>IC<sub>50</sub></b>	<b>Activity</b>
<i>Phorbas gukulensis</i>	Gukulenins A (1), B (2)	0.05-0.80 μM	Cytotoxic
<i>Aplysinopsis digitata</i>	Aplysinopliides A-C (3-5)	0.45, 0.45, and 11 μg/ml	Cytotoxic
<i>Halichondria sp.</i>	Axisonitrile 3 (6)	1.3 μM	Cytotoxic
<i>Acanthella sp.</i>	Kalihinol X (7)	9.3 μg/ml	Cytotoxic
<i>Pandoras acathifolium</i>	Pandaroside G (8) and its methyl ester (9)	t	Antimalarial, Antitrypanosomal & antileishmanial
<i>Leiodermatium sp.</i>	Leiodermatolide (10)	<10 nM	Cytotoxic *
<i>Theonella swinhoei</i>	Swinholide J (11)	6 nM	Cytotoxic
<i>Siliquariaspongia mirabilis</i>	Mirabilin (12)	0.27 μM	Cytotoxic
<i>Phorbas sp.</i>	Phorbaside C (13)	2.0 μm	Cytotoxic
<i>Plakortis sp.</i>	Leuhalide F (14), G (15)	6.2 and 5.4 μM	Cytotoxic
<i>Agelas gracilis</i>	Gracilioethers A-C (16-18)	t	Antimalarial Antileishmanial cytotoxic
<i>Petrosia sp.</i>	(-) Duryne (19-24)	0.08-0.50 μM	Cytotoxic
<i>Petrosa sp.</i>	Neopetrosoquinones A (25), B (26)	6.1-13.8 μM	Cytotoxic
<i>Mycale sp.</i>	1,5 Diazocyclohenicosane (27)	5.0-5.7 μM	Cytotoxic*
<i>Penares sp.</i>	Penasins A-E (28-32)	2-10 μg/ml	Cytotoxic
<i>Aaptos sp.</i>	Aaptamine (33-34)	5.3 and 6.7 μg/ml	Cytotoxic
<i>Monanchora pulchra</i>	Monanchocidins B-E (35-38)	110-800 nM	Cytotoxic
<i>Pseudoceratina</i>	Psammaplysin H (39)	0.41 μM	Antimalarial
<i>Ceratopsion sp.</i>	Yaku'amides A (51), B (52)	14 and 4 ng/ml	Cytotoxic
<i>Homophymia sp.</i>	Homophymine A (53)	75 nM	Cytotoxic/ antiviral
<i>Theonella sp.</i>	koshikamide B (54), C (55), H (56)	t	Cytotoxic anti-HIV
<i>T. mirabilis &amp; T. swinhoei</i>	Papuamide A (57), B (58)	3.6 ng/ml	Anti-HIV
<i>Siliquariaspongia mirabilis</i>	Celebeside A (59) & Theopapuamides B (60)	t	Anti-HIV cytotoxic
<i>T. swinhoei</i>	Perthamides C (61), D (62)	t	Anti-inflammatory
<i>T. swinhoei</i>	Solomonamide A (63)	t	Anti-inflammatory
<i>Stelletta clavosa</i>	Mirabamides E-H (64-67)	t	Anti-HIV

\* multiple cell lines † refer text

**Table 1.1: Sponge cytotoxic cyclic peptides**

<b>Source</b>	<b>Compound</b>	<b>Structure</b>	<b>Cytotoxicity</b>
Caribbean <i>Eurypon</i> <i>laughlini</i>	Rolloamide A <b>(40)</b>	-PVPLPIF-	0.4-5.8 $\mu$ M
	Rolloamide B <b>(41)</b>	-PLFPISI-	NA
Caribbean <i>Prosuberites</i> <i>laughlini</i>	Euryjanicin B <b>(42)</b>	-PPATPFV-	Mild
	Euryjanicin C <b>(43)</b>	-PLFPISI-	Mild
	Euryjanicin D <b>(44)</b>	-PIFPIFS-	Mild
Pacific <i>Stylostella sp</i> and <i>Phakellia costata</i>	Stylopeptide 1 <b>(45)</b>	-PLIFSPI-	
New Guinea <i>Stylostella sp</i>	Stylopeptide 2 <b>(46)</b>	-PYPTPFLLPF-	mild
South China <i>Phakellia fusca</i>	Phakellistatin 15 <b>(47)</b>	-PWIPLTPL-	8.5 $\mu$ M
	Phakellistatin 16 <b>(48)</b>	-PFDSRAVTY-	5.4 $\mu$ M
	Phakellistatin 17 <b>(49)</b>	-PWVPLIPI-	No activity
	Phakellistatin 18 <b>(50)</b>	-PIFPIPY-	No activity

**Table 2: Cyanobacterial metabolites**

<b>Source</b>	<b>Compound</b>	<b>IC<sub>50</sub></b>	<b>Activity</b>
<i>Lyngbya sp</i>	Bisebromoamide ( <b>68</b> )	40nM	Cytotoxic *
<i>L.majuscula</i>	Desmethoxymaj- usculamide ( <b>69</b> )	20 nM	Cytotoxic
<i>L.majuscula</i>	Hantupeptin A ( <b>70</b> )	32 nM	Cytotoxic
<i>L.majuscula</i>	Lagunamide A-C ( <b>71-73</b> )	t	Cytotoxic / antimalarial
<i>Lyngbya sp</i>	Itralamide A ( <b>74</b> ) and B ( <b>75</b> )	6 μM	Cytotoxic
<i>Lyngbya confervoides</i>	Grassypeptolide A-C ( <b>76-78</b> )	t	Cytotoxic
<i>Leptolyngbya sp</i>	Grassypeptolide D ( <b>79</b> ), E ( <b>80</b> )		
<i>Lyngbya majuscula</i>	Grassypeptolide F ( <b>81</b> ), G ( <b>82</b> )		
<i>L.majuscula</i>	Dragonamide E ( <b>83</b> )	5.1 μM	antileshmanial
<i>L.majuscula</i>	Almiramide A-C ( <b>84-86</b> )	t	antileshmanial
<i>Schizothrix</i>	Gallinamide A ( <b>87</b> )	8.4 μM 9.3 μM	Antimalarial Antileshmanial
<i>Lyngbya boulloni</i>	Alotamide ( <b>88</b> )	4.18 μM	Neurotoxin
<i>Leptolyngbya sp</i>	Coibamide A ( <b>89</b> )	2.8-7.6 nM	Cytotoxic *
<i>Leptolyngbya</i> and <i>Oscillatoria</i>	Palmyrolide A ( <b>90</b> )	5.2 μM	Neurotoxin
<i>Oscillatoria sp</i> and <i>Symploca sp</i>	Veraguamide A ( <b>91</b> ), D ( <b>92</b> ), E ( <b>93</b> )	t	Cytotoxic
<i>Oscillatoria nigro- viridis</i>	Viridamide A, B ( <b>94-95</b> )	t	Antitrypanosomal & antileshmanial
<i>Symploca</i> and <i>Oscillatoria sp</i>	Hoiamides A ( <b>96</b> ) and B ( <b>97</b> )	t	Neurotoxin
<i>Symploca sp</i>	Largazole ( <b>98</b> )	t	Cytotoxic
<i>Symploca sp</i>	Symplocamide A ( <b>99</b> )	40 nM	Cytotoxic
<i>Anabaena minutissima</i>	Minuttissamides A ( <b>100</b> )	2 μM	Cytotoxic
<i>Phormidium</i>	Caylobolide B ( <b>101</b> )	4.5-12.2 μM	Cytotoxic
<i>L. majuscula</i>	Malyngamide F ( <b>102</b> )	7-8 μM	Anti- inflammatory
<i>L.sordid</i>	Malyngamide 2 ( <b>103</b> )		

\* multiple cell lines † refer text

**Table 3: Actinomycetes cytotoxic metabolites**

Source	Compound		IC <sub>50</sub>	Activity
<i>Marinactinospora thermotolerans</i>	Marinactinones (104-106)	A-C	t	Cytotoxic
<i>Salinispora arenicola</i>	Saliniquinones (107)	A	9.9nM	cytotoxic
<i>Streptomyces albus</i>	PM050511 (108) and PM0604311 (109)		0.24-0.69 μM	Cytotoxic *
Strain NPS 693	Indoxamycins (110),F (111)	A	0.59 and 0.31 μM	Cytotoxic
<i>Streptomyces</i>	Tartrolon D (112)		8-11 μM	Cytotoxic *
<i>Cryptosphaeria sp</i>	Cryptosphaerolide (113)		4.5 μM	Cytotoxic
strain CNQ-509	Nitropyrollins (114)	D	5.7μM	Cytotoxic
<i>Actinoalloteichus cyanogriseus</i>	Caerulomycins (115)	I	0.37 μM	Cytotoxic
<i>Streptomyces</i>	Marineosins A (116), B (117)		0.5 μM and 46 μM	Cytotoxic
<i>Saccharomonospora sp</i>	Lodopyridone (118)		3.6 μM	Cytotoxic
<i>Streptomyces</i>	Ammosamides (119), B (120)	A	320 nM	Cytotoxic
<i>Streptomyces</i>	Mansouramycin (121)		0.089 μM	Cytotoxic *
<i>Salinispora arenicola</i>	Arenamide (122-124)	A-C	13.2 and 19.2μg/ml	Cytotoxic
Strain AZS17	Lobophorin C (125), Lobophorin D (126)		0.6 μg/ml and 7.5 μg/ml	Cytotoxic *

\* multiple cell lines † refer text

**Table 4: Soft coral and other metabolites**

Source	Compound	IC <sub>50</sub>	Activity
<i>Clavularia viridis</i>	Clavudrins A-D ( <b>127-130</b> )	0.16-0.88 µg/ml	Cytotoxic *
<i>Paraminabe acronephala</i>	Paraminabeolides A-D ( <b>131-134</b> )	t	Cytotoxic and anti-inflammatory
<i>Sinularia gyrosa</i>	Gyrosanols A ( <b>135</b> ), B ( <b>136</b> )	t	Antiviral Anti-inflammatory
<i>Cladiella sp</i>	Cladielloides A ( <b>137</b> ) & B ( <b>138</b> )	t	Cytotoxic and anti-inflammatory
<i>Cladiella sp</i>	Polyanthellin ( <b>139</b> )	9.02 µg/ml	-
<i>Klyxum simplex</i>	Klysimplexin ( <b>140,141</b> )	S t	Anti-inflammatory
<i>Sterospicularia laurae</i>	Asterolaurins L ( <b>142</b> )	4.0-6.2 µg/ml	Cytotoxic *
<i>Sinularia flexibis</i>	Sinulaflexiolides ( <b>143</b> ), E ( <b>144</b> )	D 8.5 and 0.12 µM	Cytotoxic
<i>Sinularia flexibilis</i>	Sinuladiterpene ( <b>145</b> )	B 8.37 µg/ml	Cytotoxic
<i>Sinularia crassa</i>	Crassarines F ( <b>146</b> ), H ( <b>147</b> )	t	Anti-inflammatory
<i>Sarcophytum crassa</i>	Sarcocrassocolide ( <b>148</b> )	I 5.1-8.4 µM	Cytotoxic *
<i>Sinulatia gibberosa</i>	Gibberosenes A ( <b>149</b> )	t	anti-inflammatory
<i>Lobophytum crassum</i>	Crassumolides ( <b>150</b> ) & C ( <b>151</b> )	A t	Anti-inflammatory
<i>Lobophytum duru</i>	Durumolides A-C ( <b>152-154</b> )	t	Anti-inflammatory Cytotoxic and antiviral
<i>Lobophytum crassum</i>	Lobocrassins B ( <b>155</b> )	t	Cytotoxic and anti-inflammatory
Brown algae/ <i>Dictyota pfaffi</i>	Dolabelladienetriol ( <b>156</b> )	t	Anti-HIV
Brown alga/ <i>Ecklonia cava</i>	6,6' Bieckol ( <b>157</b> )	1.07 µM	Anti-HIV
Indian red weed/ <i>Scinaia hatei</i> and <i>Sebdenia polydactyla</i>	Sulfated xylomannan ( <b>158</b> )	t	Anti-HSV I Anti-HSV II
Ascidian/ <i>Didemnum sp</i>	Didemnidines A ( <b>159</b> ), B ( <b>160</b> )	15 and 8.4 µM	Antimalarial
Ascidian/ <i>Pseudodistoma opacum</i>	Opacaline A ( <b>161</b> ), B ( <b>162</b> )	2.5 & 4.5 µm	Antimalarial

\* multiple cell lines † refer text

Fig 1: Chemical structures of sponge derived metabolites

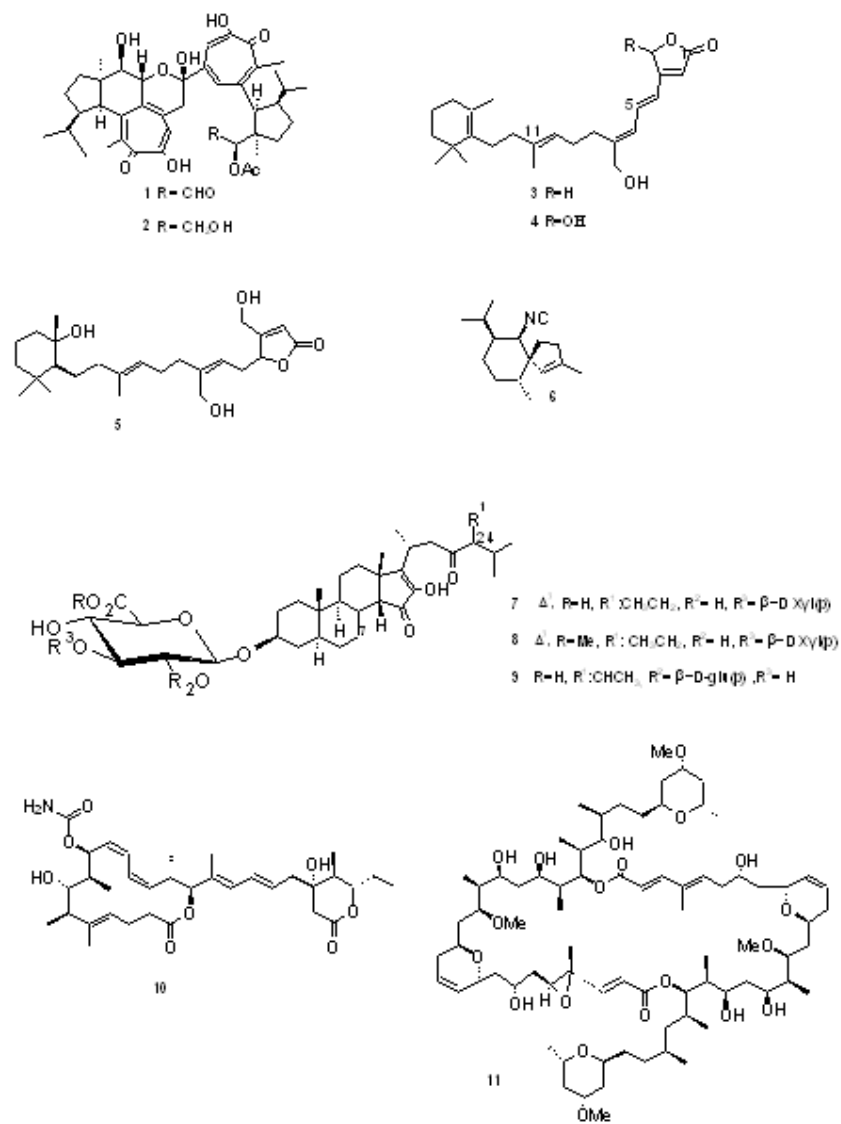
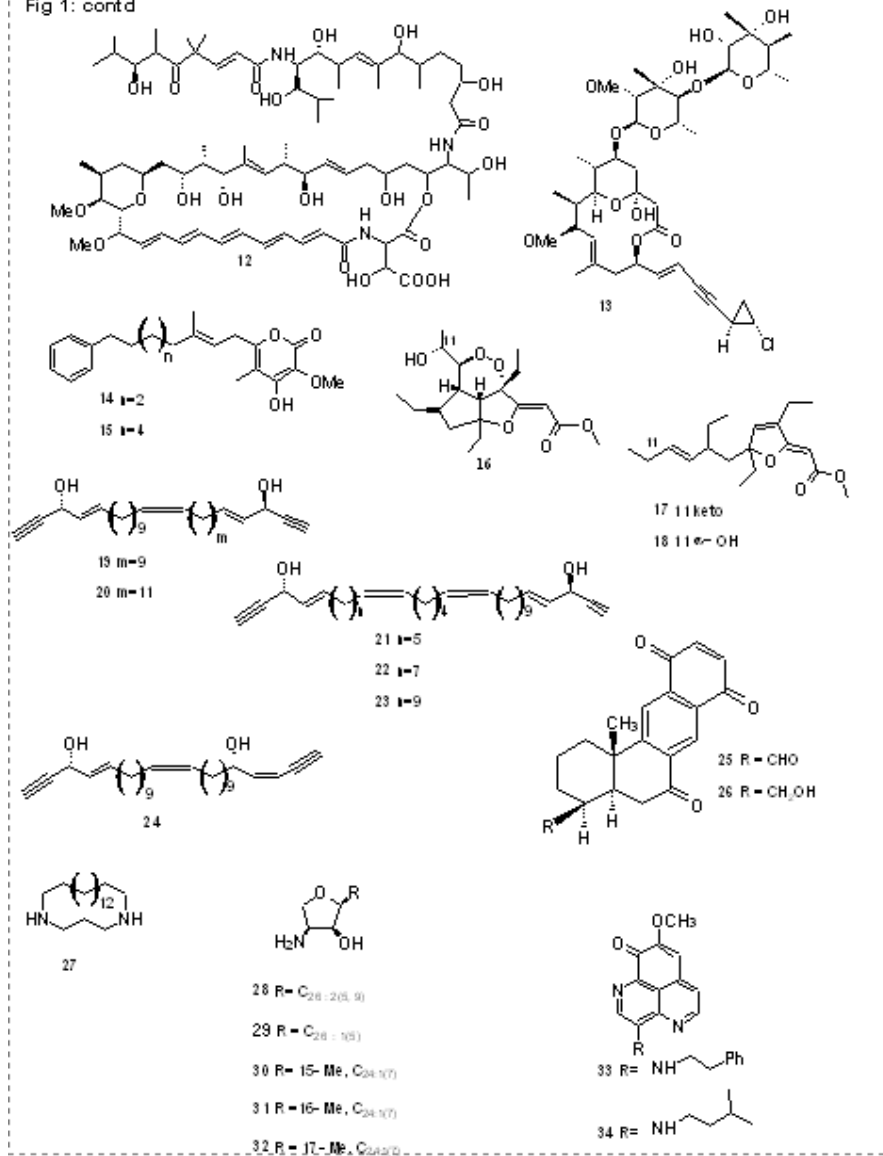




Fig 1: contd



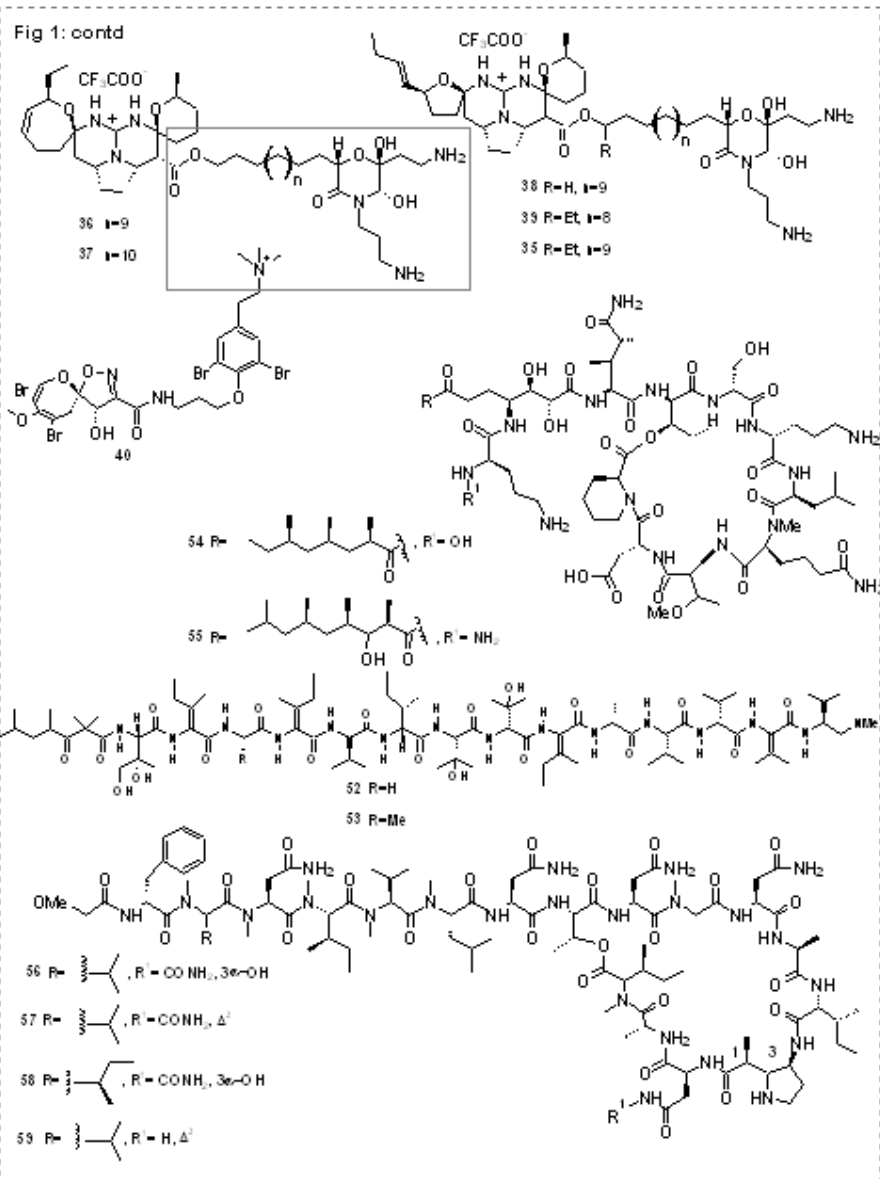


Fig 1: contd

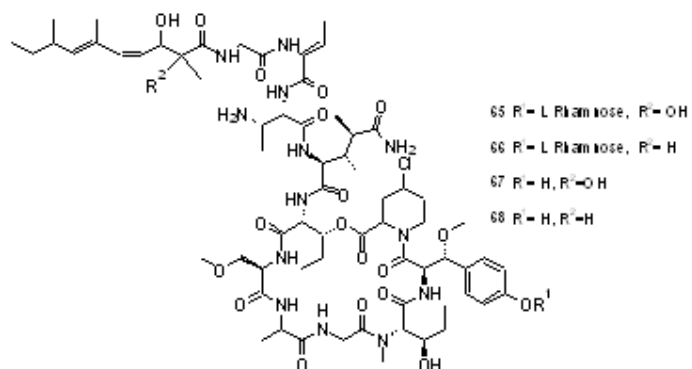
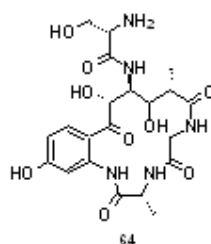
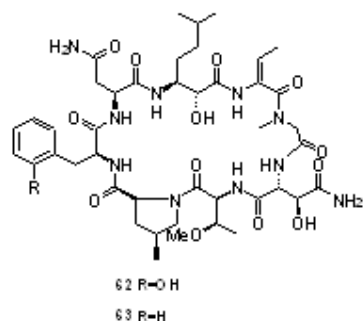
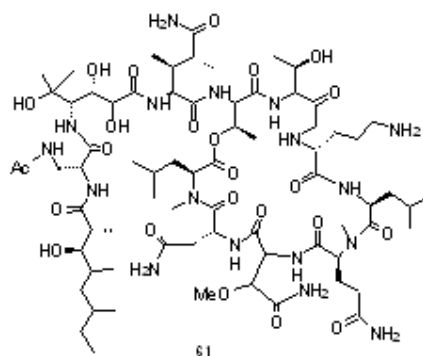
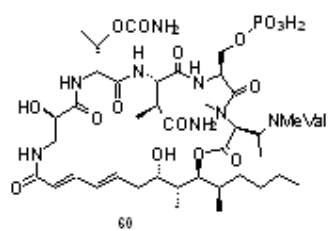


Fig 2: Chemical structures of cyanobacterial metabolites

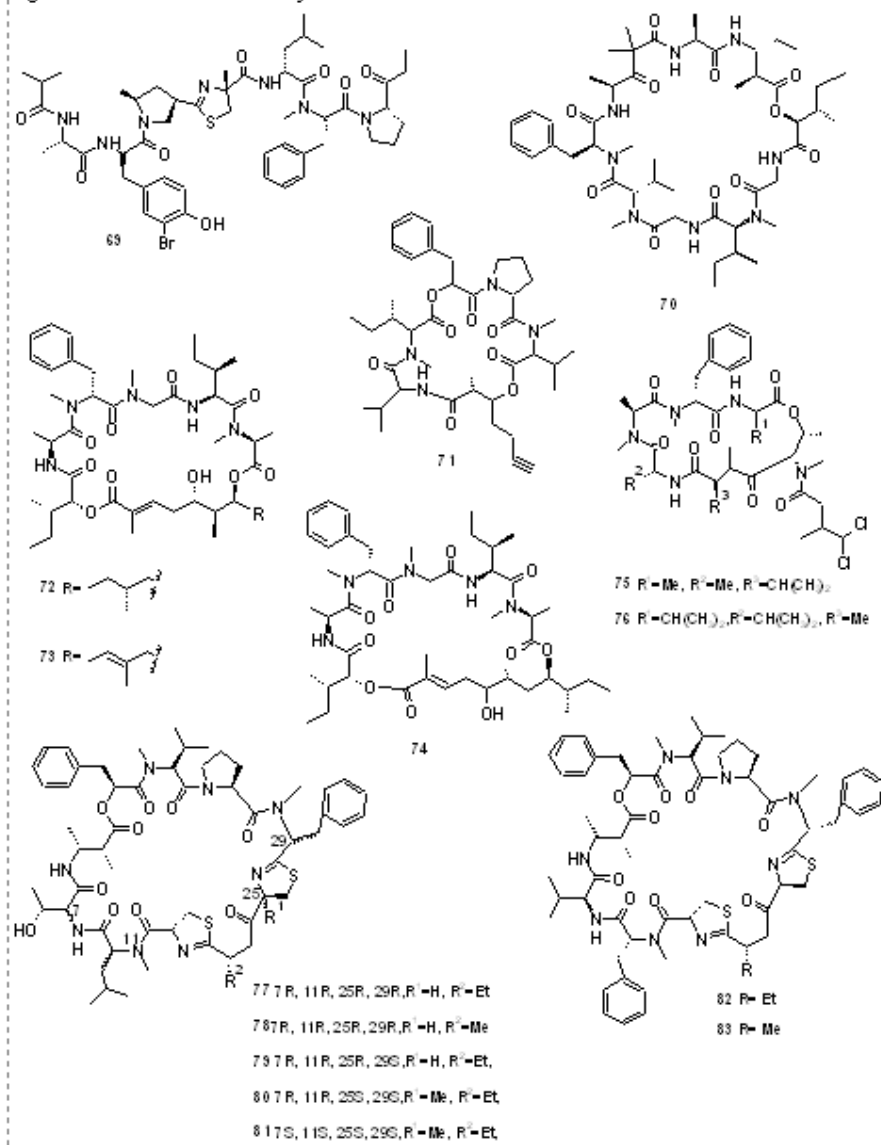


Fig 2: contd

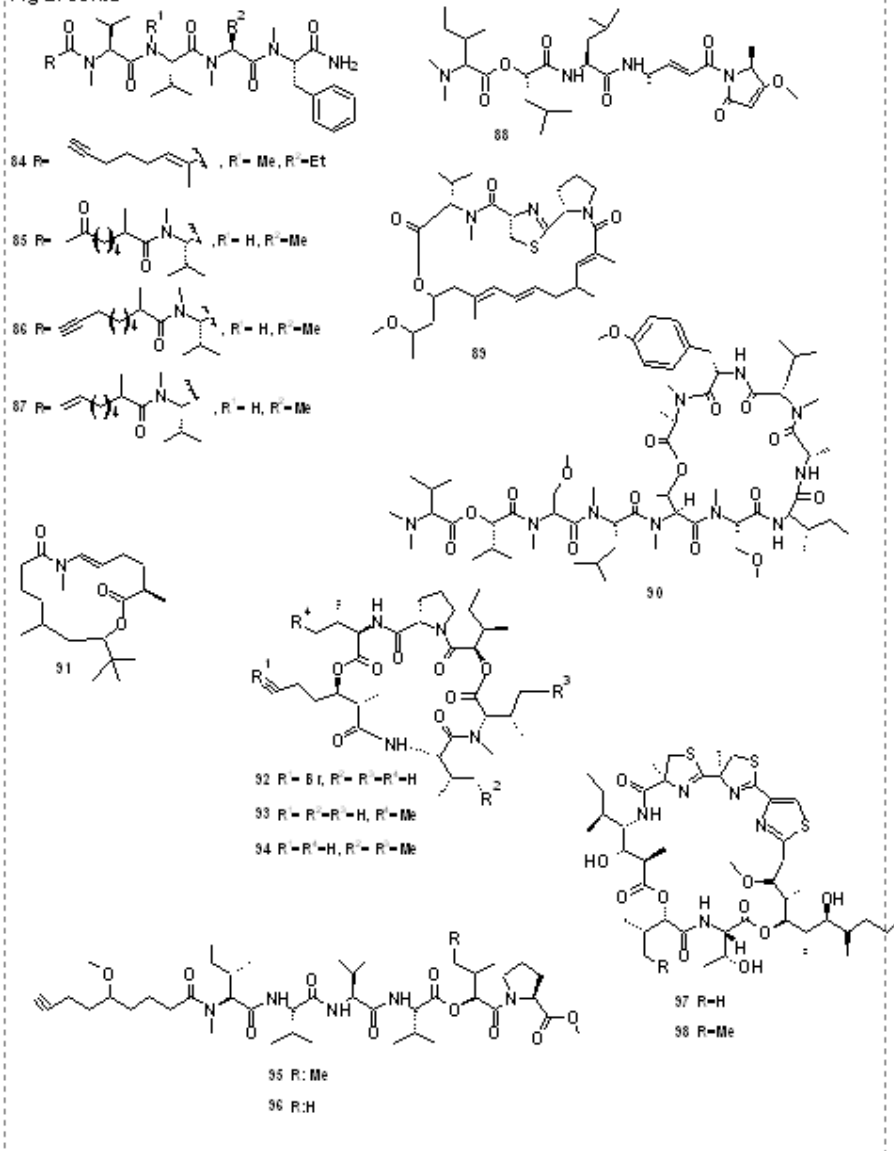


Fig 2: contd

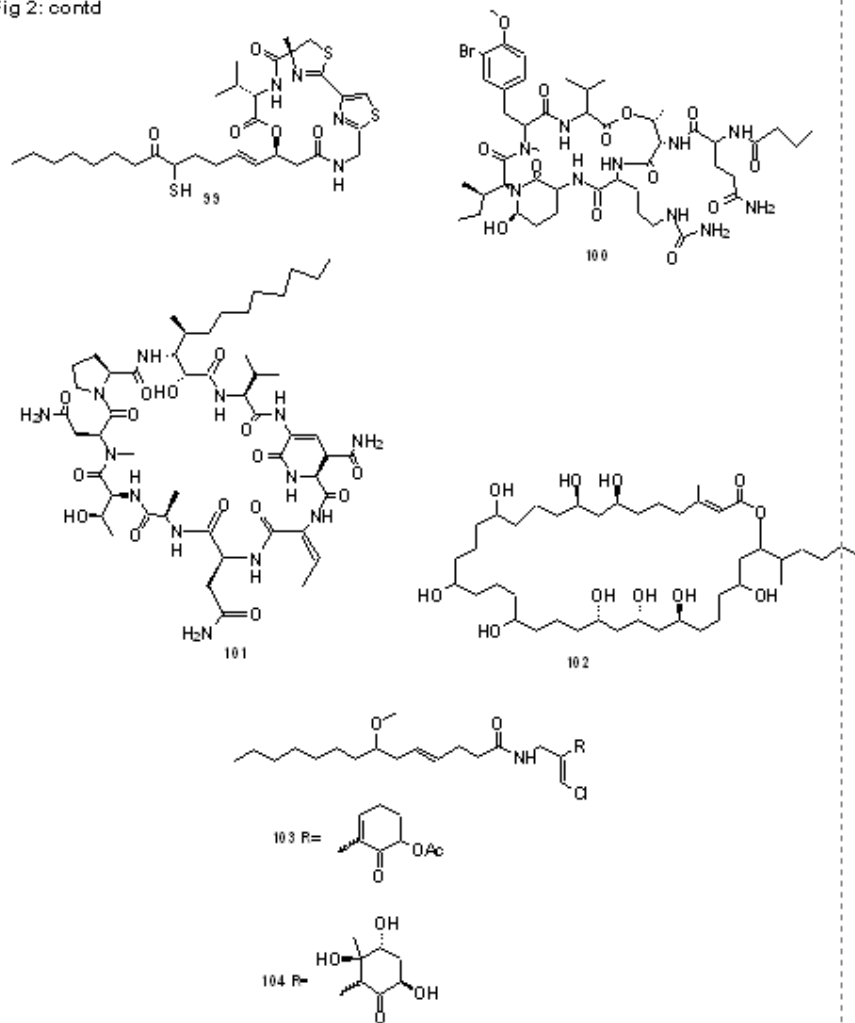


Fig 3: Chemical structures of actinomyces derived metabolites

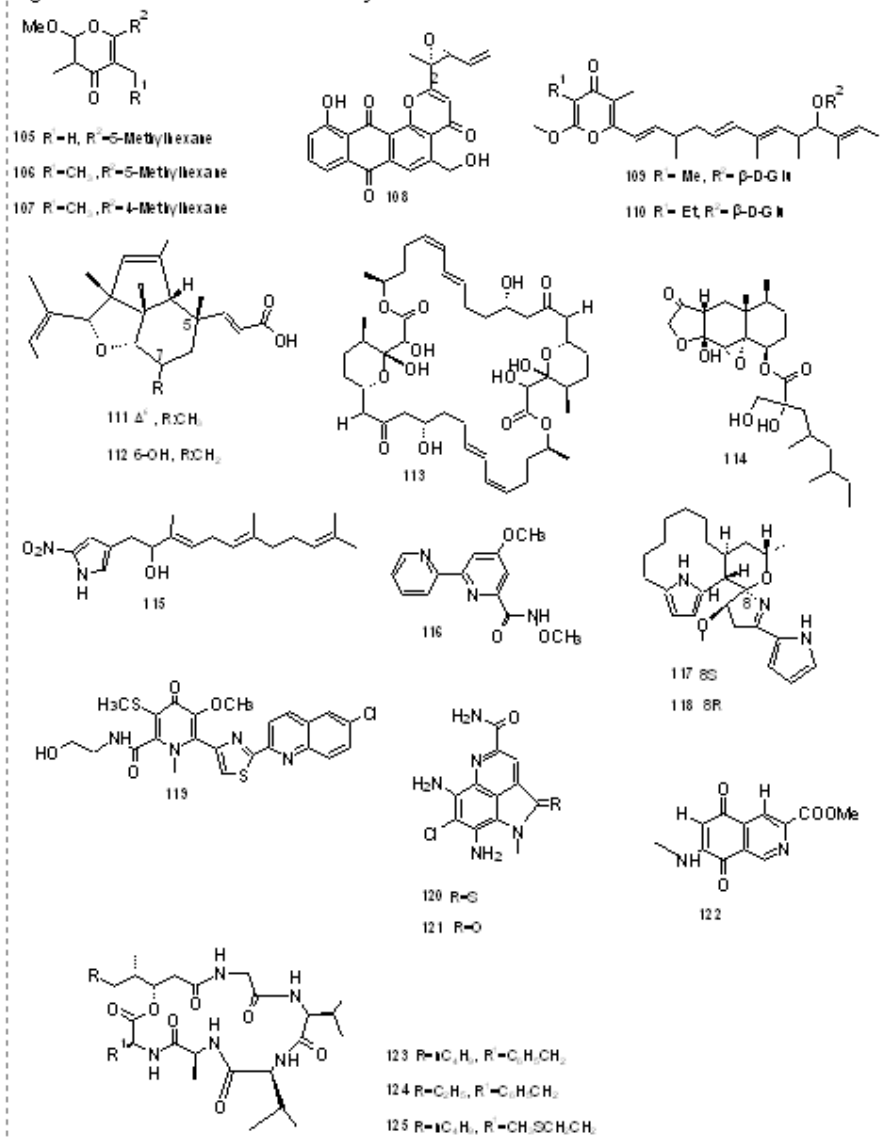


Fig 3: contd

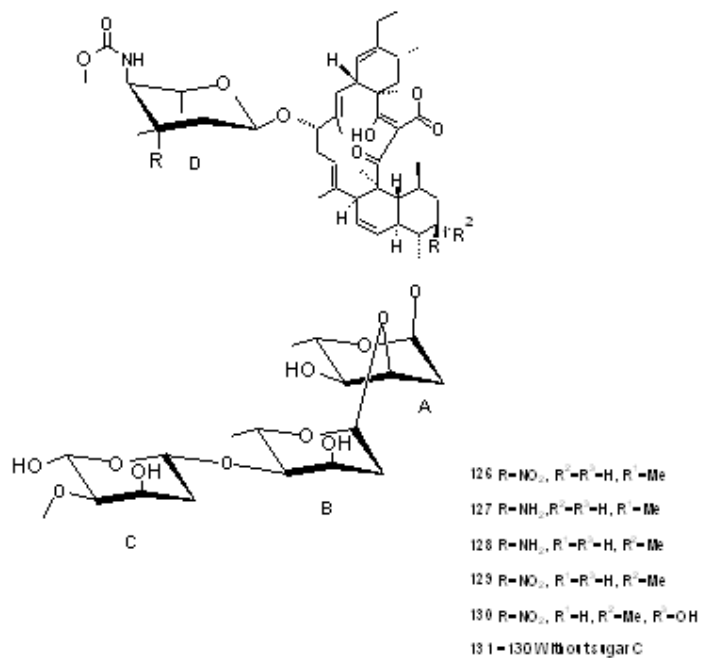




Fig 4: Chemical structures of metabolites derived from soft corals and others

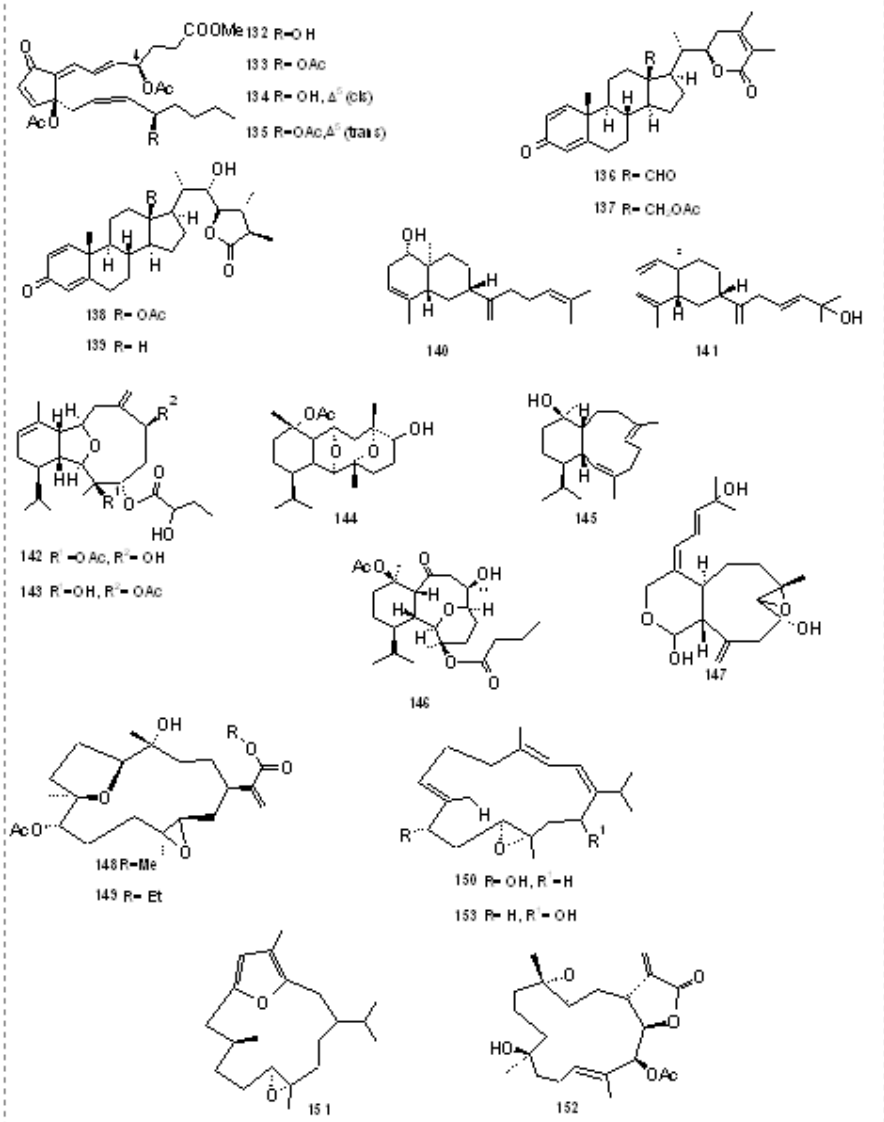
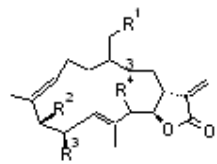


Fig 4: contd

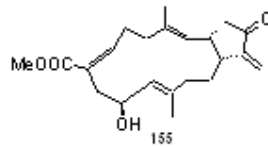


154  $\Delta^1$ , R = R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = OH

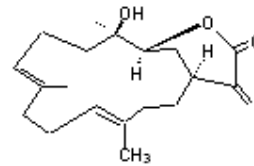
156 3-4 epoxy, R<sup>1</sup> = OAc, R<sup>2</sup> = R<sup>3</sup> = OH, R<sup>4</sup> = H

157  $\Delta^1$ , R = OAc, R<sup>2</sup> = R<sup>3</sup> = H, R<sup>4</sup> = OH

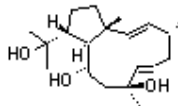
158  $\Delta^1$ , R = OH, R<sup>2</sup> = R<sup>3</sup> = H, R<sup>4</sup> = OH



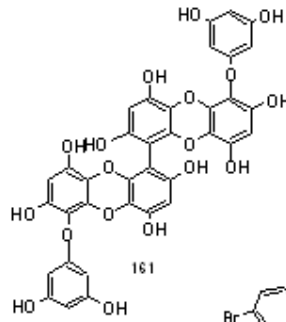
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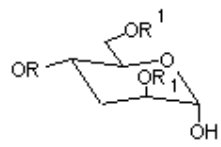
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160

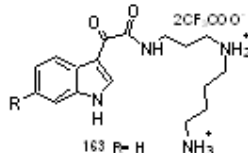


161



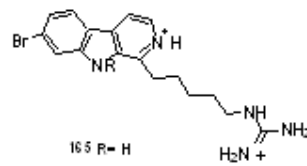
162 R = SO<sub>2</sub> or  $\beta$ -D-Xyl(p)

R<sup>1</sup> = H or  $\beta$ -D-Xyl(p)



163 R = H

164 R = Br



165 R = H

166 R = OH