Thiazole-Based Peptides

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Peptides are distinctive biomacromolecules that demonstrate potential cytotoxicity and diversified bioactivities against a variety of microorganisms including bacteria, mycobacteria, and fungi via their unique mechanisms of action. Among broad-ranging pharmacologically active peptides, natural marine-originated thiazole-based oligopeptides possess peculiar structural features along with a wide spectrum of exceptional and potent bioproperties. Because of their complex nature and size divergence, thiazole-based peptides (TBPs) bestow a pivotal chemical platform in drug discovery processes to generate competent scaffolds for regulating allosteric binding sites and peptide–peptide interactions. The present study dissertates on the natural reservoirs and exclusive structural components of marine-originated TBPs, with a special focus on their most pertinent pharmacological profiles, which may impart vital resources for the development of novel peptide-based therapeutic agents.

Keywords: azole-based peptide ; marine sponge ; peptide synthesis ; thiazole ; cytotoxicity ; cyanobacteria ; bioactivity

1. Introduction

Thiazole-based peptides (TBPs) are obtained from diverse resources, primarily from cyanobacteria, sponges, and tunicates. A thiazole ring can be part of a cyclic structure or connected in a linear chain of peptides either alone or with other heterocycles like oxazole (e.g., thiopeptide antibiotics), imidazole, and indole (in the forms of histidine and tryptophan), thiazoline, oxazoline, etc. Cyclic peptides have an advantage over their linear counterparts as cyclization offers a reduction in conformational freedom, resulting in higher receptor-binding affinities. Understanding the structure–activity relationship (SAR), different modes of action, and routes of synthesis as tools are of vital significance for the study of complex molecules like heterocyclic bioactive peptides, which have a broad spectrum of pharmacological activities associated with them. Further, the sudden increase in the number of peptide drug products is another good reason to study this particular category of compounds on a priority basis.

2. Resources

Various natural sources of TBPs and other heterocyclic rings containing cyclopolypeptides comprise cyanobacteria[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33], ascidians[34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55], marine sponges[56][57][58][59][60][61][62][63], and sea slugs[64][65][66]. Moreover, actinomycetes, sea hare, red alga, and higher plants[67][68][69][70][71][72][73] were found to be other potential resources of TBPs.

3. Biological Activity

Although thiazole-containing cyclopolypeptides of marine origin are associated with a number of bioactivities including antitubercular, antibacterial, antifungal, and inhibitory activity against serine protease enzymes chymotrypsin and elastase; anti-HIV activity; antiproliferative activity; antimalarial activity; and inhibitory activity against the transcription factor activator protein-1, the majority of them were found to exhibit anticancer activity. Various pharmacological activity-associated marine-derived Tzl-containing cyclopolypeptides along with susceptible cell line/organism with minimum inhibitory concentration are tabulated in Table 1.

Table 1. Heterocyclic Tzl-based peptides (TBPs) with diverse pharmacological activities.

TBPs	Resource	Bioactivity	
		Susceptibilty	MIC[a] Value

Haligramide A[56]	marine sponge *Haliclona nigra*	Cytotoxicity against A-549 (lung), HCT-15 (colon), SF-539 (CNS[b]), and SNB-19 (CNS) human tumor cell lines	5.17–15.62 µg/mL
Haligramide B[56]	marine sponge *Haliclona nigra*	Cytotoxicity against A-549 (lung), HCT-15 (colon), SF-539 (CNS), and SNB-19 (CNS) human tumor cells	3.89–8.82 µg/mL
Scleritodermin A[57]	marine sponge *Scleritoderma nodosum*	Cytotoxicity against colon HCT116, ovarian A2780, and breast SKBR3 cell lines	0.67–1.9 µM
Obyanamide[5]	marine cyanobacterium *Lyngbya confervoides*	Cytotoxicity against KB[c] and LoVo cells	0.58 and 3.14 µg/mL
Waiakeamide[59]	marine sponge *Ircinia dendroides*	Anti-TB activity against *Mycobacterium tuberculosis*	7.8 µg/mL
Ulongamide A[6]	marine cyanobacterium *Lyngbya* sp.	Cytotoxicity against KB and LoVo cells	1 and 5 µM
Guineamide B[7]	marine cyanobacterium *Lyngbya majuscula*	Cytotoxicity against mouse neuroblastoma cell line	15 µM
Calyxamide A[74]	marine sponge *Discodermia calyx*	Cytotoxicity against P388 murine leukemia cells	3.9 and 0.9 µM
Bistratamide J[43]	marine ascidian *Lissoclinum bistratum*	Cytotoxic activity against the human colon tumor (HCT-116) cell line	1.0 µg/mL
Didmolamide A and B[41]	marine tunicate *Didemnum molle*	Cytotoxicity against several cultured tumor cell lines (A549, HT29, and MEL28)	10–20 µg/mL
Aeruginazole A[75]	freshwater cyanobacterium *Microcystis* sp.	Antibacterial activity againt *B. subtilis* and *S. albus* Cytotoxicity against MOLT-4 human leukemia cell line and peripheral blood lymphocytes	2.2 and 8.7 µM 41 and 22.5 µM

Cyclotheonellazole A, B and C[61]	marine sponge *Theonella* aff. *swinhoei*	Inhibitory activity against serine protease enzyme chymotrypsin	0.62, 2.8, and 2.3 nM
		Inhibitory activity against serine protease enzyme elastase	0.034, 0.10, and 0.099 nM
Microcyclamide MZ602[11]	cyanobacterium *Microcystis* sp.	Inhibition activity of chymotrypsin	75 μM
Dolastatin 3[2]	marine cyanobacterium *Lyngbya majuscula*	Inhibition of HIV-1 integrase (for the terminal-cleavage and strand-transfer reactions)	5 mM and 4.1 mM
Lyngbyabellin A[20]	marine cyanobacterium *Lyngbya majuscula*	Cytotoxicity against KB cells (human nasopharyngeal carcinoma cell line) and LoVo cells (human colon adenocarcinoma cell line)	0.03 and 0.50 μg/mL
		Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	1.1 and 0.71 μM
		Cytoskeletal-disrupting effects in A-10 cells	0.01–5.0 μg/mL
Lyngbyabellin B[76]	marine cyanobacterium *Lyngbya majuscula*	Toxicity to brine shrimp (*Artemia salina*)	3.0 ppm
		Antifungal activity against *Candida albicans* (ATCC 14053) in a disk diffusion assay	100 μg/disk
		Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	1.1 and 0.71 μM
Lyngbyabellin E[21]	marine cyanobacterium *Lyngbya majuscula*	Cytotoxicity against NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cells	0.4 and 1.2 μM
		Cytoskeletal-disrupting effects in A-10 cells	0.01–6.0 μM

Lyngbyabellin H[21]	marine cyanobacterium *Lyngbya majuscula*	Cytotoxicity against NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cells	0.2 and 1.4 μM
Lyngbyabellin N[22]	marine cyanobacterium *Moorea bouilloni*	Cytotoxic activity against HCT116 colon cancer cell line	40.9 nM
27-Deoxy-lyngbyabellin A[23]	marine cyanobacterium *Lyngbya bouillonii*	Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	0.012 and 0.0073 μM
Lyngbyabellin J[23]	marine cyanobacterium *Lyngbya bouillonii*	Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	0.054 and 0.041 μM
Raocyclamide A[25]	filamentous cyanobacterium *Oscillatoria raoi*	Cytotoxicity against embryos of sea urchin *Paracentrotus lividus*	30 μg/mL (ED_{100})[d]
Tenuecyclamide A, C and D[77]	cultured cyanobacterium *Nostoc spongiaeforme* var. *tenue*	Cytotoxicity against embryos of sea urchin *Paracentrotus lividus*	10.8, 9.0, and 19.1 μM (ED_{100})
Dolastatin I[68]	sea hare *Dolabella auricularia*	Cytotoxicity against HeLa S_3 cells	12 μg/mL
		Antibacterial activities against *Micrococcus luteus*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Bacillus thuringiensis*	2.0, 8.0, 4.0, and 2.0 μg/mL
Marthiapeptide A[67]	marine actinomycete *Marinactinospora thermotolerans* SCSIO 00652	Cytotoxicity against SF-268 (human glioblastoma) cell line, MCF-7 (human breast adenocarcinoma) cell line, NCI-H460 (human lung carcinoma) cell line, and HepG2 (human hepatocarcinoma) cancer cell line	0.38, 0.43, 0.47, and 0.52 μM
Keramamide G, H and J[60]	marine sponge *Theonella* sp.	Cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells	10 μg/mL

Keramamide K[78]	marine sponge *Theonella* sp.	Cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells	0.72 and 0.42 µg/mL
Lissoclinamide 8[48]	sea squirt *Lissoclinum patella*	Cytotoxicity against T24 (bladder carcinoma cells), MRC5CV1 (fibroblasts), and lymphocytes	6, 1, and 8 µg/mL
Mechercharmycin A[72]	marine bacterium *Thermoactinomyces* sp. YM3-251	Cytotoxic activity against A549 (human lung cancer) cells and Jurkat cells (human leukemia)	4.0×10^{-8} M and 4.6×10^{-8} M
Leucamide A[63]	marine sponge *Leucetta microraphis*	Cytotoxicity against HM02, HepG2, and Huh7 tumor cell lines	5.2, 5.9, and 5.1 µg/mL
Bistratamide H[47]	marine ascidian *Lissoclinum bistratum*	Cytotoxic activity against the human colon tumor (HCT-116) cell line	1.7 µg/mL
Patellamide E[51]	marine ascidian *Lissoclinum patella*	Cytotoxicity against human colon tumor cells in vitro	125 µg/mL
Microcyclamide[28]	cultured cyanobacterium *Microcystis aeruginosa*	Cytotoxicity against P388 murine leukemia cells	1.2 µg/mL
Dolastatin E[69]	sea hare *Dolabella auricularia*	Cytotoxicity against HeLa-S_3 cells	22–40 µg/mL
Aerucyclamide A[31]	freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806	Antiparasite activity against *Plasmodium falciparum* K1 and *Trypanosoma brucei rhodesiense* STIB 900	5.0 and 56.3 µM
Aerucyclamide B[31]	freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806	Antiparasite activity against *Plasmodium falciparum* K1 and *Trypanosoma brucei rhodesiense* STIB 900	0.7 and 15.9 µM
Aerucyclamide C[31]	freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806	Antiparasite activity against *Plasmodium falciparum* K1 and *Trypanosoma brucei rhodesiense* STIB 900	2.3 and 9.2 µM

Aerucyclamide D[31]	freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806	Antiparasite activity against *Plasmodium falciparum* K1 and *Trypanosoma brucei rhodesiense* STIB 900	6.3 and 50.1 μM
Aerucyclamide A, B and C[30][31]	freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806	Grazer toxicity against the freshwater crustacean *Thamnocephalus platyurus*	30.5, 33.8, and 70.5 μM
Aerucyclamide B and C[31]	freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806	Cytotoxic activity against Rat Myoblast L6 cells	120 and 106 μM
Urukthapelstatin A[71]	marine-derived bacterium *Mechercharimyces asporophorigenens* YM11-542	Cytotoxicity against A549 human lung cancer cells	12 nM
Mechercharmycin A[72]	marine-derived bacterium *Thermoactinomyces* sp.	Cytotoxicity against A549 human lung cancer cells and Jurkat cells	4.0×10^{-8} M and 4.6×10^{-8} M
Ulithiacyclamide[49][79]	marine tunicate *Lissoclinum patella*	Cytotoxic activity against L1210, MRC5CV1, T24, and CEM cell lines (continuous exposure)	0.35, 0.04, 0.10, and 0.01 μg/mL
Ulicyclamide[79]	marine tunicate *Lissoclinum patella*	Cytotoxic activity against L1210 murine leukemia cells	7.2 μg/mL
Patellamide A[79]	marine tunicate *Lissoclinum patella*	Cytotoxic activity against L1210 murine leukemia and human ALL cell line (CEM)	3.9 and 0.028 μg/mL
Patellamide B, C[79]	marine tunicate *Lissoclinum patella*	Cytotoxic activity against L1210 murine leukemia cells	2.0 and 3.2 μg/mL
Venturamide A[27]	marine cyanobacterium *Oscillatoria* sp.	Antiparasitic activity against *Plasmodium falciparum, Trypanasoma cruzi* Cytotoxicity against mammalian Vero cells and MCF-7 cancer cells	8.2 and 14.6 μM 86 and 13.1 μM

Venturamide B[27]	marine cyanobacterium *Oscillatoria* sp.	Antiparasitic activity against *Plasmodium falciparum, Trypanasoma cruzi* Cytotoxicity against mammalian Vero cells	5.2 and 15.8 μM 56 μM
Bistratamides A and B[53]	aplousobranch ascidian *Lissoclinum bistratum*	Cytotoxicity against MRC5CV1 fibroblasts and T24 bladder carcinoma cells	50 and 100 μg/mL
Bistratamide M[54]	marine ascidian *Lissoclinum bistratum*	Cytotoxicity against breast, colon, lung, and pancreas cell lines	18, 16, 9.1, and 9.8 μM
Balgacyclamide A[26]	freshwater cyanobacterium *Microcystis aeruguinosa* EAWAG 251	Antimalarial activity against *Plasmodium falciparum* K1	9 and 59 μM
Balgacyclamide B[26]	freshwater cyanobacterium *Microcystis aeruguinosa* EAWAG 251	Antiparasitic activity against *Trypanosoma brucei rhodesiense* STIB 900	8.2 and 51 μM

[a] MIC—minimum inhibitory concentration, [b] CNS—central nervous system, [c] KB—ubiquitous KERATIN-forming tumor cell subline, [d] ED_{100}—effective dose for 100% inhibition.

References

1. Adiv, S.; Ahronov-Nadborny, R.; Carmeli, S. New aeruginazoles, a group of thiazole-containing cyclic peptides from Microcystis aeruginosa blooms. Tetrahedron 2012, 68, 1376–1383.
2. Mitchell, S.S.; Faulkner, D.J.; Rubins, K.; Bushman, F.D. Dolastatin 3 and two novel cyclic peptides from a Palauan collection of Lyngbya majuscula. J. Nat. Prod. 2000, 63, 279–282.
3. McIntosh, J.A.; Lin, Z.; Tianero, M.D.; Schmidt, E.W. Aestuaramides, a natural library of cyanobactin cyclic peptides resulting from isoprene-derived Claisen rearrangements. ACS Chem. Biol. 2013, 8, 877–883.
4. Ploutno, A.; Carmeli, S. Modified peptides from a water bloom of the cyanobacterium Nostoc sp. Tetrahedron 2002, 58, 9949–9957.
5. Williams, P.G.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. Isolation and structure determination of obyanamide, a novel cytotoxic cyclic depsipeptide from the marine cyanobacterium Lyngbya confervoides. J. Nat. Prod. 2002, 65, 29–31.
6. Luesch, H.; Williams, P.G.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. Ulongamides A-F, new beta-amino acid-containing cyclodepsipeptides from Palauan collections of the marine cyanobacterium Lyngbya sp. J. Nat. Prod. 2002, 65, 996–1000.
7. Tan, L.T.; Sitachitta, N.; Gerwick, W.H. The guineamides, novel cyclic depsipeptides from a Papua New Guinea collection of the marine cyanobacterium Lyngbya majuscula. J. Nat. Prod. 2003, 66, 764–771.
8. Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. New apratoxins of marine cyanobacterial origin from Guam and Palau. Bioorg. Med. Chem. 2002, 10, 1973–1978.
9. Hong, J.; Luesch, H. Largazole: From discovery to broad-spectrum therapy. Nat. Prod. Rep. 2012, 29, 449–456.
10. Sudek, S.; Haygood, M.G.; Youssef, D.T.A.; Schmidt, E.W. Structure of Trichamide, a cyclic peptide from the bloom-forming cyanobacterium Trichodesmium erythraeum, predicted from the genome sequence. Appl. Environ. Microbiol. 2006, 72, 4382–4387.

11. Zafrir-Ilan, E.; Carmeli, S. Two new microcyclamides from a water bloom of the cyanobacterium Microcystis sp. Tetrahedron Lett. 2010, 51, 6602–6604.

12. Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J.; Corbett, T.H. Total structure determination of apratoxin A, a potent novel cytotoxin from the marine cyanobacterium Lyngbya majuscula. J. Am. Chem. Soc. 2001, 123, 5418–5423.

13. Gutiérrez, M.; Suyama, T.L.; Engene, N.; Wingerd, J.S.; Matainaho, T.; Gerwick, W.H. Apratoxin D, a potent cytotoxic cyclodepsipeptide from papua new guinea collections of the marine cyanobacteria Lyngbya majuscule and Lyngbya sordida. J. Nat. Prod. 2008, 71, 1099–1103.

14. Matthew, S.; Schupp, P.J.; Luesch, H. Apratoxin E, a cytotoxic peptolide from a Guamanian collection of the marine cyanobacterium Lyngbya bouillonii. J. Nat. Prod. 2008, 71, 1113–1116.

15. Tidgewell, K.; Engene, N.; Byrum, T.; Media, J.; Doi, T.; Valeriote, F.A.; Gerwick, W.H. Evolved diversification of a modular natural product pathway: Apratoxins F and G, two cytotoxic cyclic depsipeptides from a Palmyra collection of Lyngbya bouillonii. ChemBioChem 2010, 11, 1458–1466.

16. Thornburg, C.C.; Cowley, E.S.; Sikorska, J.; Shaala, L.A.; Ishmael, J.E.; Youssef, D.T.A.; McPhail, K.L. Apratoxin H and apratoxin A sulfoxide from the Red sea cyanobacterium Moorea producens. J. Nat. Prod. 2013, 76, 1781–1788.

17. Kwan, J.C.; Ratnayake, R.; Abboud, K.A.; Paul, V.J.; Luesch, H. Grassypeptolides A−C, cytotoxic bis-thiazoline containing marine cyclodepsipeptides. J. Org. Chem. 2010, 75, 8012–8023.

18. Thornburg, C.C.; Thimmaiah, M.; Shaala, L.A.; Hau, A.M.; Malmo, J.M.; Ishmael, J.E.; Youssef, D.T.A.; McPhail, K.L. Cyclic depsipeptides, grassypeptolides D, E and Ibu epidemethoxylyngbyastatin 3, from a Red sea Leptolyngbya cyanobacterium. J. Nat. Prod. 2011, 74, 1677–1685.

19. Popplewell, W.L.; Ratnayake, R.; Wilson, J.A.; Beutler, J.A.; Colburn, N.H.; Henrich, C.J.; McMahon, J.B.; McKee, T.C. Grassypeptolides F and G, cyanobacterial peptides from Lyngbya majuscula. J. Nat. Prod. 2011, 74, 1686–1691.

20. Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J.; Mooberry, S.L. Isolation, Structure determination, and biological activity of lyngbyabellin A from the marine cyanobacterium Lyngbya majuscula. J. Nat. Prod. 2000, 63, 611–615.

21. Han, B.; McPhail, K.L.; Gross, H.; Goeger, D.E.; Mooberry, S.L.; Gerwick, W.H. Isolation and structure of five lyngbyabellin derivatives from a Papua New Guinea collection of the marine cyanobacterium Lyngbya majuscula. Tetrahedron 2005, 61, 11723–11729.

22. Choi, H.; Mevers, E.; Byrum, T.; Valeriote, F.A.; Gerwick, W.H. Lyngbyabellins K-N from two Palmyra Atoll collections of the marine cyanobacterium Moorea bouilloni. Eur. J. Org. Chem. 2012, 2012(27), 5141–5150.

23. Matthew, S.; Salvador, L.A.; Schupp, P.J.; Paul, V.J.; Luesch, H. Cytotoxic halogenated macrolides and modified peptides from the apratoxin-producing marine cyanobacterium Lyngbya bouillonii from Guam. J. Nat. Prod. 2010, 73, 1544–1552.

24. Soria-Mercado, I.E.; Pereira, A.; Cao, Z.; Murray, T.F.; Gerwick, W.H. Alotamide A, a novel neuropharmacological agent from the marine cyanobacterium Lyngbya bouillonii. Org. Lett. 2009, 11, 4704–4707.

25. Admi, V.; Afek, U.; Carmeli, S. Raocyclamides A and B, novel cyclic hexapeptides isolated from the cyanobacterium Oscillatoria raoi. J. Nat. Prod. 1996, 59, 396–399.

26. Portmann, C.; Sieber, S.; Wirthensohn, S.; Blom, J.F.; Da Silva, L.; Baudat, E.; Kaiser, M.; Brun, R.; Gademann, K. Balgacyclamides, antiplasmodial heterocyclic peptides from Microcystis aeruguinosa EAWAG 251. J. Nat. Prod. 2014, 77, 557–562.

27. Linington, R.G.; González, J.; Ureña, L.-D.; Romero, L.I.; Ortega-Barría, E.; Gerwick, W.H. Venturamides A and B: Antimalarial constituents of the Panamanian marine cyanobacterium Oscillatoria sp. J. Nat. Prod. 2007, 70, 397–401.

28. Ishida, K.; Nakagawa, H.; Murakami, M. Microcyclamide, a cytotoxic cyclic hexapeptide from the cyanobacterium Microcystis aeruginosa. J. Nat. Prod. 2000, 63, 1315–1317.

29. Jüttner, F.; Todorova, A.K.; Walch, N.; von Philipsborn, W. Nostocyclamide M: A cyanobacterial cyclic peptide with allelopathic activity from Nostoc 31. Phytochemistry 2001, 57, 613–619.

30. Portmann, C.; Blom, J.F.; Gademann, K.; Jüttner, F. Aerucyclamides A and B: Isolation and synthesis of toxic ribosomal heterocyclic peptides from the cyanobacterium Microcystis aeruginosa PCC 7806. J. Nat. Prod. 2008, 71, 1193–1196.

31. Portmann, C.; Blom, J.F.; Kaiser, M.; Brun, R.; Jüttner, F.; Gademann, K. Isolation of aerucyclamides C and D and structure revision of microcyclamide 7806A: Heterocyclic ribosomal peptides from Microcystis aeruginosa PCC 7806 and their antiparasite evaluation. J. Nat. Prod. 2008, 71, 1891–1896.

32. Chuang, P.-H.; Hsieh, P.-W.; Yang, Y.-L.; Hua, K.-F.; Chang, F.-R.; Shiea, J.; Wu, S.-H.; Wu, Y.-C. Cyclopeptides with anti-inflammatory activity from seeds of Annona montana. J. Nat. Prod. 2008, 71, 1365–1370.

33. Ogino, J.; Moore, R.E.; Patterson, G.M.L.; Smith, C.D. Dendroamides, new cyclic hexapeptides from a blue-green alga. Multidrug-resistance reversing activity of dendroamide A. J. Nat. Prod. 1996, 59, 581–586.

34. McDonald, L.A.; Foster, M.P.; Phillips, D.R.; Ireland, C.M.; Lee, A.Y.; Clardy, J. Tawicyclamides A and B, new cyclic peptides from the ascidian Lissoclinum patella: Studies on the solution- and solid-state conformations. J. Org. Chem. 1992, 57, 4616–4624.

35. Arrault, A.; Witczak-Legrand, A.; Gonzalez, P.; Bontemps-Subielos, N.; Banaigs, B. Structure and total synthesis of cyclodidemnamide B, a cycloheptapeptide from the ascidian Didemnum molle. Tetrahedron Lett. 2002, 43, 4041–4044.

36. Carroll, A.R.; Bowden, B.F.; Coll, J.C.; Hockless, D.C.R.; Skelton, B.W.; White, A.H. Studies of Australian ascidians. IV. Mollamide, a cytotoxic cyclic heptapeptide from the compound ascidian Didemnum molle. Aust. J. Chem. 1994, 47, 61–69.

37. Carroll, A.R.; Coll, J.C.; Bourne, J.C.; MacLeod, J.K.; Zanriskie, T.M.; Ireland, C.M.; Bowden, B.F. Patellins 1-6 and trunkamide A: Novel cyclic hexa-, hepta- and octa-peptides from colonial ascidians, Lissoclinum sp. Aust. J. Chem. 1996, 49, 659–667.

38. Rudi, A.; Aknin, M.; Gaydou, E.M.; Kashman, Y. Four new cytotoxic cyclic hexa- and heptapeptides from the marine ascidian Didemnum molle. Tetrahedron 1998, 54, 13203–13210.

39. Donia, M.S.; Wang, B.; Dunbar, D.C.; Desai, P.V.; Patny, A.; Avery, M.; Hamann, M.T. Mollamides B and C, cyclic hexapeptides from the Indonesian tunicate Didemnum molle. J. Nat. Prod. 2008, 71, 941–945.

40. Lu, Z.; Harper, M.K.; Pond, C.D.; Barrows, L.R.; Ireland, C.M.; Van Wagoner, R.M. Thiazoline peptides and a tris-phenethyl urea from Didemnum molle with anti-HIV activity. J. Nat. Prod. 2012, 75, 1436–1440.

41. Rudi, A.; Chill, L.; Aknin, M.; Kashman, Y. Didmolamide A and B, two new cyclic hexapeptides from the marine ascidian Didemnum molle. J. Nat. Prod. 2003, 66, 575–577.

42. Teruya, T.; Sasaki, H.; Suenaga, K. Hexamollamide, a hexapeptide from an Okinawan ascidian Didemnum molle. Tetrahedron Lett. 2008, 49, 5297–5299.

43. Perez, L.J.; Faulkner, D.J. Bistratamides E-J, modified cyclic hexapeptides from the Philippines ascidian Lissoclinum bistratum. J. Nat. Prod. 2003, 66, 247–250.

44. Fu, X.; Do, T.; Schmitz, F.J.; Andrusevich, V.; Engel, M.H. New cyclic peptides from the ascidian Lissoclinum patella. J. Nat. Prod. 1998, 61, 1547–1551.

45. Morris, L.A.; Jantina Kettenes van den Bosch, J.; Versluis, K.; Thompson, G.S.; Jaspars, M. Structure determination and MSn analysis of two new lissoclinamides isolated from the Indo-Pacific ascidian Lissoclinum patella: NOE restrained molecular dynamics confirms the absolute stereochemistry derived by degradative methods. Tetrahedron 2000, 56, 8345–8353.

46. Ireland, C.; Scheuer, P.J. Ulicyclamide and ulithiacyclamide, two new small peptides from a marine tunicate. J. Am. Chem. Soc. 1980, 102, 5688–5691.

47. Rashid, M.A.; Gustafson, K.R.; Cardellina II, J.H.; Boyd, M.R. Patellamide F, a new cytotoxic cyclic peptide from the colonial ascidian Lissoclinum patella. J. Nat. Prod. 1995, 58, 594–597.

48. Hawkins, C.J.; Lavin, M.F.; Marshall, K.A.; Van den Brenk, A.L.; Watters, D.J. Structure-activity relationships of the lissoclinamides: Cytotoxic cyclic peptides from the ascidian Lissoclinum patella. J. Med. Chem. 1990, 33, 1634–1638.

49. Degnan, B.M.; Hawkins, C.J.; Lavin, M.F.; McCaffrey, E.J.; Parry, D.L.; Van den Brenk, A.L.; Watters, D.J. New cyclic peptides with cytotoxic activity from the ascidian Lissoclinum patella. J. Med. Chem. 1989, 32, 1349–1354.

50. Williams, D.E.; Moore, R.E. The structure of ulithiacyclamide B. Antitumor evaluation of cyclic peptides and macrolides from Lissoclinum patella. J. Nat. Prod. 1989, 52, 732–739.

51. McDonald, L.A.; Ireland, C.M. Patellamide E: A new cyclic peptide from the ascidian Lissoclinum patella. J. Nat. Prod. 1992, 55, 376–379.

52. Foster, M.P.; Concepcion, G.P.; Caraan, G.B.; Ireland, C.M. Bistratamides C and D. two new oxazole-containing cyclic hexapeptides isolated from a Philippine Lissoclinum bistratum ascidian. J. Org. Chem. 1992, 57, 6671–6675.

53. Degnan, B.M.; Hawkins, C.J.; Lavin, M.F.; McCaffrey, E.J.; Parry, D.L.; Watters, D.J. Novel cytotoxic compounds from the ascidian Lissoclinum bistratum. J. Med. Chem. 1989, 32, 1354–1359.

54. Urda, C.; Fernández, R.; Rodríguez, J.; Pérez, M.; Jiménez, C.; Cuevas, C. Bistratamides M and N, oxazole-thiazole containing cyclic hexapeptides isolated from Lissoclinum bistratum interaction of zinc (II) with bistratamide K. Mar. Drugs 2017, 15, 209.

55. Toske, S.G.; Fenical, W. Cyclodidemnamide: A new cyclic heptapeptide from the marine ascidian Didemnum molle. Tetrahedron Lett. 1995, 36, 8355–8358.

56. Rashid, M.A.; Gustafson, K.R.; Boswell, J.L.; Boyd, M.R. Haligramides A and B, two new cytotoxic hexapeptides from the marine sponge Haliclona nigra. J. Nat. Prod. 2000, 63, 956–959.

57. Schmidt, E.W.; Raventos-Suarez, C.; Bifano, M.; Menendez, A.T.; Fairchild, C.R.; Faulkner, D.J. Scleritodermin A, a cytotoxic cyclic peptide from the Lithistid sponge Scleritoderma nodosum. J. Nat. Prod. 2004, 67, 475–478.

58. Chill, L.; Kashman, Y.; Schleyer, M. Oriamide, a new cytotoxic cyclic peptide containing a novel amino acid from the marine sponge Theonella sp. Tetrahedron 1997, 53, 16147–16152.

59. Mau, C.M.S.; Nakao, Y.; Yoshida, W.Y.; Scheuer, P.J. Waiakeamide, a cyclic hexapeptide from the sponge Ircinia dendroides. J. Org. Chem. 1996, 61, 6302–6304.

60. Kobayashi, J.; Itagaki, F.; Shigemori, I.; Takao, T.; Shimonishi, Y. Keramamides E, G, H, and J, new cyclic peptides containing an oxazole or a thiazole ring from a Theonella sponge. Tetrahedron 1995, 51, 2525–2532.

61. Issac, M.; Aknin, M.; Gauvin-Bialecki, A.; De Voogd, N.; Ledoux, A.; Frederich, M.; Kashman, Y.; Carmeli, S. Cyclotheonellazoles A–C, potent protease inhibitors from the marine sponge Theonella aff. swinhoei. J. Nat. Prod. 2017, 80, 1110–1116.

62. Erickson, K.L.; Gustafson, K.R.; Milanowski, D.J.; Pannell, L.K.; Klose, J.R.; Boyd, M.R. Myriastramides A–C, new modified cyclic peptides from the Philippines marine sponge Myriastra clavosa. Tetrahedron 2003, 59, 10231–10238.

63. Kehraus, S.; König, G.M.; Wright, A.D.; Woerheide, G. Leucamide A: A new cytotoxic heptapeptide from the Australian sponge Leucetta microraphis. J. Org. Chem. 2002, 67, 4989–4992

64. Tan, K.O.; Wakimoto, T.; Takada, K.; Ohtsuki, T.; Uchiyama, N.; Goda, Y.; Abe, I. Cycloforskamide, a cytotoxic macrocyclic peptide from the sea slug Pleurobranchus forskalii. J. Nat. Prod. 2013, 76, 1388–1391.

65. Wesson, K.J.; Hamann, M.T. Keenamide A, a bioactive cyclic peptide from the marine mollusk Pleurobranchus forskalii. J. Nat. Prod. 1996, 59, 629–631.

66. Dalisay, D.S.; Rogers, E.W.; Edison, A.S.; Molinski, T.F. Structure elucidation at the nanomole scale. 1. Trisoxazole macrolides and thiazole-containing cyclic peptides from the nudibranch Hexabranchus sanguineus. J. Nat. Prod. 2009, 72, 732–738

67. Zhou, X.; Huang, H.; Chen, Y.; Tan, J.; Song, Y.; Zou, J.; Tian, X.; Hua, Y.; Ju, J. Marthiapeptide A, an anti-infective and cytotoxic polythiazole cyclopeptide from a 60 L scale fermentation of the deep sea-derived Marinactinospora thermotolerans SCSIO 00652. J. Nat. Prod. 2012, 75, 2251–2255.

68. Sone, H.; Kigoshi, H.; Yamada, K. Isolation and stereostructure of dolastatin I, a cytotoxic cyclic hexapeptide from the Japanese sea hare Dolabella auricularia. Tetrahedron 1997, 53, 8149–8154.

69. Ojika, M.; Nemoto, T.; Nakamura, M.; Yamada, K. Dolastatin E, a new cyclic hexapeptide isolated from the sea hare Dolabella auricularia. Tetrahedron Lett. 1995, 36, 5057–5058.

70. Tan, L.T.; Williamson, R.T.; Gerwick, W.H.; Watts, K.S.; McGough, K.; Jacobs, R. cis, cis- and trans, trans-Ceratospongamide, new bioactive cyclic heptapeptides from the Indonesian red alga Ceratodictyon spongiosum and symbiotic sponge Sigmadocia symbiotica. J. Org. Chem. 2000, 65, 419–425.

71. Matsuo, Y.; Kanoh, K.; Yamori, T.; Kasai, H.; Katsuta, A.; Adachi, K.; Shin-ya, K.; Shizuri, Y. Urukthapelstatin A, a novel cytotoxic substance from marine-derived Mechercharimyces asporophorigenens YM11-542. J. Antibiot. 2007, 60, 251–255.

72. Kanoh, K.; Matsuo, Y.; Adachi, K.; Imagawa, H.; Nishizawa, M.; Shizuri, Y. Mechercharmycins A and B, cytotoxic substances from marine-derived Thermoactinomyces sp. YM3-251. J. Antibiot. 2005, 58, 289–292.

73. Itokawa, H.; Yun, Y.; Morita, H.; Takeya, K.; Yamada, K. Estrogen-like activity of cyclic peptides from Vaccaria segetalis extracts. Planta Med. 1995, 61, 561–562.

74. Miki Kimura; Toshiyuki Wakimoto; Yoko Egami; Karen Co Tan; Yuji Ise; Ikuro Abe; Calyxamides A and B, Cytotoxic Cyclic Peptides from the Marine Sponge Discodermia calyx. *Journal of Natural Products* **2012**, *75*, 290-294, 10.1021/np2009187.

75. Avi Raveh; Shmuel Carmeli; Aeruginazole A, a Novel Thiazole-Containing Cyclopeptide from the CyanobacteriumMicrocystissp.. *Organic Letters* **2010**, *12*, 3536-3539, 10.1021/ol1014015.

76. Hendrik Luesch; Wesley Y. Yoshida; Richard E. Moore; Valerie J. Paul; Isolation and structure of the cytotoxin lyngbyabellin B and absolute configuration of lyngbyapeptin A from the marine cyanobacterium Lyngbya majuscula.. *Journal of Natural Products* **2000**, *63*, 1437-1439, 10.1021/np000104n.

77. Ronny Banker; Shmuel Carmeli; Tenuecyclamides A−D, Cyclic Hexapeptides from the CyanobacteriumNostocspongiaeformevar.tenue. *Journal of Natural Products* **1998**, *61*, 1248-1251, 10.1021/np980138j.

78. Hiroshi Uemoto; Yumi Yahiro; Hideyuki Shigemori; Masashi Tsuda; Toshifumi Takao; Yasutsugu Shimonishi; Jun'ichi Kobayashi; Keramamides K and L, new cyclic peptides containing unusual tryptophan residue from Theonella sponge. *Tetrahedron* **1998**, *54*, 6719-6724, 10.1016/s0040-4020(98)00358-5.

79. Chris M. Ireland; Augustine R. Durso; Robert A. Newman; Miles P. Hacker; Antineoplastic cyclic peptides from the marine tunicate Lissoclinum patella. *The Journal of Organic Chemistry* **1982**, *47*, 1807-1811, 10.1021/jo00349a002.