

Thiazole-Based Peptides

Subjects: [Chemistry, Medicinal](#) | [Pharmacology & Pharmacy](#)

Contributor: Rajiv Dahiya , Sunita Dahiya , Neeraj Kumar Fuloria , Suresh Kumar , Rita Mourya , Suresh V. Chennupati , Satish Jankie , Hemendra Gautam , Sunil Singh , Sanjay Kumar Karan , Sandeep Maharaj , Shivkanya Fuloria , Jyoti Shrivastava , Alka Agarwal , Shamjeet Singh , Awadh Kishor , Gunjan Jadon , Ajay Sharma

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.

[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 cyclopeptides 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 cyclopeptides 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 cyclopeptides 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	
		Susceptibility	MIC ^a Value
Haligramide A ^[56]	marine sponge	Cytotoxicity against A-549 (lung),	5.17–15.62
	<i>Haliclona nigra</i>	HCT-15 (colon), SF-539 (CNS ^b), and SNB-19 (CNS) human tumor cell lines	µg/mL
Haligramide B ^[56]	marine sponge	Cytotoxicity against A-549 (lung),	3.89–8.82
	<i>Haliclona nigra</i>	HCT-15 (colon), SF-539 (CNS), and SNB-19 (CNS) human tumor cells	µg/mL

Scleritodermin A ^[57]	marine sponge <i>Scleritoderma nodosum</i>	Cytotoxicity against colon HCT116, ovarian A2780, and breast SKBR3 cell lines	0.67–1.9 μ M
Obyanamide ^[5]	marine cyanobacterium <i>Lyngbya confervoides</i>	Cytotoxicity against KB ^c and LoVo cells	0.58 and 3.14 μ g/mL
Waiakeamide ^[59]	marine sponge <i>Ircinia dendroides</i>	Anti-TB activity against <i>Mycobacterium tuberculosis</i>	7.8 μ g/mL
Ulongamide A ^[6]	marine cyanobacterium <i>Lyngbya</i> sp.	Cytotoxicity against KB and LoVo cells	1 and 5 μ M
Guineamide B ^[7]	marine cyanobacterium <i>Lyngbya majuscula</i>	Cytotoxicity against mouse neuroblastoma cell line	15 μ M
Calyxamide A ^[74]	marine sponge <i>Discodermia calyx</i>	Cytotoxicity against P388 murine leukemia cells	3.9 and 0.9 μ M
Bistratamide J ^[43]	marine ascidian <i>Lissoclinum bistratum</i>	Cytotoxic activity against the human colon tumor (HCT-116) cell line	1.0 μ g/mL
Didmolamide A and B ^[41]	marine tunicate <i>Didemnum molle</i>	Cytotoxicity against several cultured tumor cell lines (A549, HT29, and MEL28)	10–20 μ g/mL

Aeruginazole A ^[75]	freshwater cyanobacterium	Antibacterial activity against <i>B. subtilis</i> and <i>S. albus</i>	2.2 and 8.7 μ M
	<i>Microcystis</i> sp.	Cytotoxicity against MOLT-4 human leukemia cell line and peripheral blood lymphocytes	41 and 22.5 μ M
Cyclotheonellazole A, B and C ^[61]	marine sponge	Inhibitory activity against serine protease enzyme chymotrypsin	0.62, 2.8, and 2.3 nM
	<i>Theonella</i> aff. <i>swinhoei</i>	Inhibitory activity against serine protease enzyme elastase	0.034, 0.10, and 0.099 nM
Microcyclamide MZ602 ^[11]	cyanobacterium	Inhibition activity of	75 μ M
	<i>Microcystis</i> sp.	chymotrypsin	
Dolastatin 3 ^[2]	marine cyanobacterium	Inhibition of HIV-1 integrase (for the terminal-cleavage and strand-	5 mM
	<i>Lyngbya majuscula</i>	transfer reactions)	and 4.1 mM
Lyngbyabellin A ^[20]	marine cyanobacterium <i>Lyngbya majuscula</i>	Cytotoxicity against KB cells (human nasopharyngeal carcinoma cell line) and LoVo cells (human colon adenocarcinoma cell line)	0.03 and 0.50 μ g/mL

		Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	1.1 and 0.71 μ M
		Cytoskeletal-disrupting effects in A-10 cells	0.01–5.0 μ g/mL
Lyngbyabellin B ^[76]	marine cyanobacterium <i>Lyngbya majuscula</i>	Toxicity to brine shrimp (<i>Artemia salina</i>)	3.0 ppm
		Antifungal activity against <i>Candida albicans</i> (ATCC 14053) in a disk diffusion assay	100 μ g/disk
		Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	1.1 and 0.71 μ M
Lyngbyabellin E ^[21]	marine cyanobacterium <i>Lyngbya majuscula</i>	Cytotoxicity against NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cells	0.4 and 1.2 μ M
		Cytoskeletal-disrupting effects in A-10 cells	0.01–6.0 μ M
Lyngbyabellin H ^[21]	marine cyanobacterium <i>Lyngbya majuscula</i>	Cytotoxicity against NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cells	0.2 and 1.4 μ M

Lyngbyabellin N ^[22]	marine cyanobacterium <i>Moorea bouillonii</i>	Cytotoxic activity against HCT116 colon cancer cell line	40.9 nM
27-Deoxy-lyngbyabellin A ^[23]	marine cyanobacterium <i>Lyngbya bouillonii</i>	Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	0.012 and 0.0073 μ M
Lyngbyabellin J ^[23]	marine cyanobacterium <i>Lyngbya bouillonii</i>	Cytotoxicity against HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells	0.054 and 0.041 μ M
Raocyclamide A ^[25]	filamentous cyanobacterium <i>Oscillatoria raoi</i>	Cytotoxicity against embryos of sea urchin <i>Paracentrotus lividus</i>	30 μ g/mL (ED ₁₀₀) ^d
Tenuecyclamide A, C and D ^[77]	cultured cyanobacterium <i>Nostoc spongiaeforme</i> var. <i>tenu</i>	Cytotoxicity against embryos of sea urchin <i>Paracentrotus lividus</i>	10.8, 9.0, and 19.1 μ M (ED ₁₀₀)
Dolastatin I ^[68]	sea hare <i>Dolabella auricularia</i>	Cytotoxicity against HeLa S ₃ cells	12 μ g/mL
Marthiapeptide A ^[67]	marine actinomycete <i>Marinactinospora thermotolerans</i> SCSIO 00652	Antibacterial activities against <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , and <i>Bacillus thuringiensis</i>	2.0, 8.0, 4.0, and 2.0 μ g/mL

		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 μ M
Keramamide G, H and J ^[60]	marine sponge <i>Theonella</i> sp.	Cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells	10 μ g/mL
Keramamide K ^[78]	marine sponge <i>Theonella</i> sp.	Cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells	0.72 and 0.42 μ g/mL
Lissoclinamide 8 ^[48]	sea squirt <i>Lissoclinum patella</i>	Cytotoxicity against T24 (bladder carcinoma cells), MRC5CV1 (fibroblasts), and lymphocytes	6, 1, and 8 μ g/mL
Mechercharmycin A ^[72]	marine bacterium <i>Thermoactinomyces</i> 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	Cytotoxicity against HM02, HepG2, and Huh7	5.2, 5.9, and 5.1 μ g/mL

	<i>Leucetta microraphis</i>	tumor cell lines	
Bistratamide H ^[47]	marine ascidian <i>Lissoclinum bistratum</i>	Cytotoxic activity against the human colon tumor (HCT-116) cell line	1.7 µg/mL
Patellamide E ^[51]	marine ascidian <i>Lissoclinum patella</i>	Cytotoxicity against human colon tumor cells in vitro	125 µg/mL
Microcyclamide ^[28]	cultured cyanobacterium <i>Microcystis aeruginosa</i>	Cytotoxicity against P388 murine leukemia cells	1.2 µg/mL
Dolastatin E ^[69]	sea hare <i>Dolabella auricularia</i>	Cytotoxicity against HeLa-S ₃ cells	22–40 µg/mL
Aerucyclamide A ^[31]	freshwater cyanobacterium <i>Microcystis aeruginosa</i> PCC 7806	Antiparasite activity against <i>Plasmodium falciparum</i> K1 and <i>Trypanosoma brucei rhodesiense</i> STIB 900	5.0 and 56.3 µM
Aerucyclamide B ^[31]	freshwater cyanobacterium <i>Microcystis aeruginosa</i> PCC 7806	Antiparasite activity against <i>Plasmodium falciparum</i> K1 and <i>Trypanosoma brucei rhodesiense</i>	0.7 and 15.9 µM

		STIB 900	
Aerucyclamide C ^[31]	freshwater cyanobacterium <i>Microcystis aeruginosa</i> PCC 7806	Antiparasite activity against <i>Plasmodium falciparum</i> K1 and <i>Trypanosoma brucei rhodesiense</i> STIB 900	2.3 and 9.2 μM
Aerucyclamide D ^[31]	freshwater cyanobacterium <i>Microcystis aeruginosa</i> PCC 7806	Antiparasite activity against <i>Plasmodium falciparum</i> K1 and <i>Trypanosoma brucei rhodesiense</i> STIB 900	6.3 and 50.1 μM
Aerucyclamide A, B and C ^[30] ^[31]	freshwater cyanobacterium <i>Microcystis aeruginosa</i> PCC 7806	Grazer toxicity against the freshwater crustacean <i>Thamnocephalus platyurus</i>	30.5, 33.8, and 70.5 μM
Aerucyclamide B and C ^[31]	freshwater cyanobacterium <i>Microcystis aeruginosa</i> PCC 7806	Cytotoxic activity against Rat Myoblast L6 cells	120 and 106 μM
Urukthapelstatin A ^[71]	marine-derived bacterium <i>Mechercharimyces asporophorigenens</i> YM11-542	Cytotoxicity against A549 human lung cancer cells	12 nM
Mechercharmycin A ^[72]	marine-derived bacterium <i>Thermoactinomyces</i> 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 <i>Lissoclinum patella</i>	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 <i>Lissoclinum patella</i>	Cytotoxic activity against L1210 murine leukemia cells	7.2 µg/mL
Patellamide A ^[79]	marine tunicate <i>Lissoclinum patella</i>	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 <i>Lissoclinum patella</i>	Cytotoxic activity against L1210 murine leukemia cells	2.0 and 3.2 µg/mL
Venturamide A ^[27]	marine	Antiparasitic activity against <i>Plasmodium falciparum</i> , <i>Trypanosoma cruzi</i>	8.2 and 14.6 µM
	cyanobacterium <i>Oscillatoria</i> sp.	Cytotoxicity against mammalian Vero cells and MCF-7 cancer cells	86 and 13.1 µM
Venturamide B ^[27]	marine	Antiparasitic activity against <i>Plasmodium falciparum</i> , <i>Trypanosoma cruzi</i>	5.2 and 15.8 µM
	cyanobacterium <i>Oscillatoria</i> sp.	Cytotoxicity against mammalian Vero cells	56 µM

Bistratamides A and B ^[53]	aplousobranch	Cytotoxicity against MRC5CV1 fibroblasts and T24 bladder carcinoma cells	50 and 100 µg/mL
	ascidian		
	<i>Lissoclinum bistratum</i>		
Bistratamide M ^[54]	marine ascidian	Cytotoxicity against breast, colon, lung, and pancreas cell lines	18, 16, 9.1, and 9.8 µM
	<i>Lissoclinum bistratum</i>		
Balgacyclamide A ^[26]	freshwater cyanobacterium	Antimalarial activity against <i>Plasmodium falciparum</i> K1	9 and 59 µM
	<i>Microcystis aeruginosa</i> EAWAG 251		
Balgacyclamide B ^[26]	freshwater cyanobacterium	Antiparasitic activity against <i>Trypanosoma brucei</i>	8.2 and 51 µM
	<i>Microcystis aeruginosa</i> EAWAG 251	<i>rhodesiense</i> STIB 900	

^a MIC—minimum inhibitory concentration, ^b CNS—central nervous system, ^c KB—ubiquitous KERATIN-forming tumor cell subline, ^d ED₁₀₀—effective dose for 100% inhibition.

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