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Review Article

Unexplored Marine-Derived Microbial Metabolites as Next-Generation Antiparasitic Agents: Phytochemistry, Mechanistic Insights, and Translational Prospects

Ishita Debnath[1], Suman Ghosh[2,*], Nirjhar Duttagupta[2], Sitanshu Mondal[2], Jitendra Debata[2], Sumit Nandi[3], Soumik Bhattacharjee[3], Rana Dutta[3], Sajal Kumar Jha[4], Nabanita Banik[4], Mithun Bhowmik[5], Arindam Chatterjee[6], Sudip Roy[7], Ayantika Sil[8], Amites Gangopadhyay[9], Avijit Ghosh[10], Samar Patra[10], Shubhajit Das[10], Disha Das[10], Piyush Mahato[10], Bapan Khan[10]

[1]Department of Pharmaceutical Chemistry, Bengal College of Pharmaceutical Sciences and Research, Durgapur, West Bengal, INDIA.
[2]Department of Pharmaceutical Chemistry, Bengal College of Pharmaceutical Technology, Dubrajpur, West Bengal, INDIA.
[3]Department of Pharmacology, Gupta College of Technological Sciences, Asansol, West Bengal, INDIA.
[4]Department of Pharmaceutics, Bengal College of Pharmaceutical Technology, Dubrajpur, West Bengal, INDIA.
[5]Department of Pharmaceutics, Bengal College of Pharmaceutical Sciences and Research, Durgapur, West Bengal, INDIA.
[6]Department of Pharmaceutics, Gupta College of Technological Sciences, Asansol, West Bengal, INDIA.
[7]Department of Pharmaceutics, NSHM Institute of Pharmaceutical Technology, NSHM Knowledge Campus, Durgapur, West Bengal, INDIA.
[8]Department of Pharmaceutical Technology, Gupta College of Technological Sciences, Asansol, West Bengal, INDIA.
[9]Department of Pharmaceutical Chemistry, Gupta College of Technological Sciences, Asansol, West Bengal, INDIA.
[10]Department of Pharmaceutical Science, Bengal College of Pharmaceutical Technology, Dubrajpur, West Bengal, INDIA.

ABSTRACT

Background: Marine-derived microbial metabolites have emerged as an underexplored but exceptionally promising source of antiparasitic agents. Over the past two decades, intensive efforts in natural product discovery have revealed structurally unique compounds ranging from alkaloids, peptides, and polyketides to glycolipids and nucleoside analogues that exhibit potent activity against protozoan and helminthic parasites. In this review, we systematically evaluated the phytochemical diversity, pharmacological mechanisms, and toxicological considerations of these marine metabolites, with emphasis on compounds targeting *Plasmodium, Leishmania, Trypanosoma, Toxoplasma, Entamoeba,* and *Schistosoma* species. **Materials and Methods:** This review systematically collated and critically analyzed published literature from PubMed, Scopus, and Web of Science focusing on marine microbial metabolites with antiparasitic activity. Data were integrated on phytochemical classes, biosynthetic origins, mechanisms of action, *in vitro* and *in vivo* efficacy, selectivity indices, toxicological evaluations, and translational feasibility. **Results:** Diverse compounds including alkaloids (manzamine A, renieramycin A), nucleoside analogues (tubercidin), β-lactones (salinosporamide A), lipodepsipeptides (gallinamide A), and glycolipids (sulfoquinovosyl diacylglycerols) demonstrated potent activity against protozoan and helminthic parasites, with IC_{50} values ranging from nanomolar to low micromolar. Mechanistic insights revealed proteasome inhibition, cysteine protease blockade, DNA synthesis interference, mitochondrial disruption, and membrane destabilization as key antiparasitic strategies. Preclinical studies indicated encouraging selectivity indices and tolerable host cytotoxicity for several scaffolds. **Conclusion:** Marine microbial metabolites constitute a chemically diverse and pharmacologically valuable frontier for antiparasitic drug discovery. By integrating phytochemistry, pharmacology, and toxicology, this review highlights their translational potential and emphasizes future directions including biosynthetic engineering, SAR-guided analog design, and standardized *in vivo* validation to accelerate progression into clinical pipelines.

Keywords: Antiparasitic Agents, Marine Microbial Metabolites, Pharmacology, Phytochemistry, Toxicology.

Correspondence:
Mr. Suman Ghosh
Department of Pharmaceutical Chemistry, Bengal College of Pharmaceutical Technology, Dubrajpur-731123, West Bengal, INDIA.
Email: ghoshsuman280@gmail.com
ORCID: 0009-0005-6321-9733

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INTRODUCTION

Marine macroalgae also known as seaweeds represent a vast, multifaceted, and largely untapped reservoir of natural bioactive compounds with significant therapeutic potential (Monroy-García *et al*., 2025). These multicellular photosynthetic organisms, encompassing brown (Phaeophyceae), red (Rhodophyta), and green (Chlorophyta) lineages, thrive across diverse marine environments and have evolved remarkable chemical defenses against predators, microbial pathogens, and environmental stressors (L. Pereira, 2021; Premarathna *et al*., 2022). This evolutionary pressure has endowed them with complex secondary metabolites, including polyphenols, sulfated polysaccharides, carotenoids, terpenoids, and peptides that possess potent biological activities such as antioxidant, antiviral, anti-inflammatory, and notably, antiparasitic effects

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(Kumar *et al.*, 2021; Leandro *et al.*, 2019). Despite considerable exploration of macroalgae for applications in nutraceuticals and oncology, their role in controlling parasitic diseases remains underexplored (Adarshan *et al.*, 2023). Increasing resistance to frontline antiparasitic agents for diseases such as malaria, leishmaniasis, Chagas disease, and schistosomiasis underscores the urgent necessity for novel chemical scaffolds with alternative mechanisms of action (Njoroge *et al.*, 2014). Marine macroalgae and their microbial metabolites offer a promising frontier in this context, providing both novel chemical diversity and ecological sustainability (Vicente *et al.*, 2021). Traditional usage of certain seaweed species as deworming agents, such as *Digenea simplex* against human intestinal nematodes, and the nematocidal properties found in *Notheia anomala* extracts illustrate the ethnopharmacological relevance of these organisms (Bonde *et al.*, 2021). More recently, *in vivo* and *in vitro* studies have confirmed significant antiparasitic activity from cold-water brown algae species (e.g., *Laminaria digitata, Saccharina latissima*) against gastrointestinal nematodes like *Ascaris suum* and *Teladorsagia circumcincta* (Bonde *et al.*, 2023). Moreover, compounds such as Sulfoquinovosyl Diacylglycerols (SQDGs) identified in *Lobophora variegata* demonstrate potent inhibition of anaerobic protozoa including *Giardia intestinalis, Entamoeba histolytica*, and *Trichomonas vaginalis* (Cantillo-Ciau *et al.*, 2010). These findings highlight the functional relevance of macroalgal metabolites against a broad spectrum of parasitic taxa and emphasize their potential as sources of antiparasitic drug leads. However, sustainability challenges, such as low natural abundance, inefficient extraction protocols, and variable compound yields, have hindered systematic drug discovery efforts from macroalgae. Advances in green extraction technologies, aquaculture systems, and synthetic biology are now offering viable solutions to these limitations (Nurkolis, 2025; Samoraj *et al.*, 2024). This review aims to comprehensively explore the phytochemistry, pharmacology, and toxicological attributes of marine macroalgal metabolites with demonstrated anti-parasitic activity. This review also elaborates current knowledge across redox-stressed habitats, analyze structure-activity relationships of key compounds, and critically assess translational feasibility, including extraction scalability, mechanistic targets, and cytotoxicity profiles.

SURVEY OF ANTIPARASITIC MARINE MICROBIAL METABOLITES

Marine Microbial Metabolites Active Against Pathogenic Protozoa

Marine microbial ecosystems represent a prolific and evolutionarily distinct reservoir of secondary metabolites with broad-spectrum activity against human protozoan pathogens such as *Plasmodium, Trypanosoma, Leishmania*, and *Toxoplasma gondii*. These parasites, responsible for a significant global disease burden, particularly in tropical and developing regions, exhibit increasing drug resistance and necessitate new therapeutic scaffolds. Marine-derived actinomycetes, cyanobacteria, and sponge-associated bacteria have yielded structurally unique compounds including alkaloids, depsipeptides, nucleoside analogs, and polyketides, each with targeted or multitarget anti-protozoal actions (Ameen *et al.*, 2021; Davies-Bolorunduro *et al.*, 2021).

Ionophoric and Kinase-Inhibiting Depsipeptides: Valinomycin and Staurosporine

Valinomycin, a cyclic dodecadepsipeptide produced by *Streptomyces* spp. from Mediterranean sponges, demonstrates potent ionophoric activity by disrupting mitochondrial potassium gradients, leading to loss of membrane potential and parasite death. It is highly active against *T. brucei* ($IC_{50} \approx 3.2$ nM) and *Leishmania major* ($IC_{50} < 110$ nM), exhibiting a selectivity index (SI) >100 (Andersson *et al.*, 1998; *New Molecular Entities and Structure–Activity Relationships of Drugs Designed by the Natural Product Derivatization Method from 2010 to 2018*, 2021). Staurosporine, an indolocarbazole also from marine *Streptomyces*, inhibits protein kinases in *T. brucei* ($IC_{50} \approx 5.3$ µM), affecting cell cycle progression and inducing apoptosis via caspase-like pathways (Stepczynska *et al.*, 2001). Both represent bioactive leads with defined mechanisms, though staurosporine's moderate host toxicity remains a developmental constraint.

Broad-Spectrum Nucleoside Analogue: Tubercidin and Derivatives

Tubercidin, a C7-deazaadenosine analog from marine *Streptomyces* and sponge symbionts, disrupts purine salvage pathways essential in protozoan parasites. It exhibits potent inhibition across *Trypanosoma brucei, Trypanosoma cruzi, Leishmania* spp., and *Toxoplasma gondii*, with IC_{50} values between 0.06-0.30 µM. Tubercidin-treated murine models showed complete clearance of bloodstream trypanosomes without notable toxicity (Drew *et al.*, 2003). However, its non-specificity toward mammalian purine transporters necessitates prodrug development or derivatization. 3′-deoxytubercidin analogs are under evaluation for improved selectivity (Fiuza *et al.*, 2022).

Mitochondrial Disruptors: Renieramycin A and Araguspongin C

Renieramycin A, a tetrahydroisoquinoline alkaloid from *Xestospongia* spp., exhibits anti-leishmanial activity with an $IC_{50} \approx 0.2$ µg/mL. Araguspongin C, another sponge alkaloid, induces parasite clearance in *L. donovani*-infected hamsters (~39% reduction in liver burden) (Fang *et al.*, 2021). These compounds act primarily through mitochondrial membrane disruption and ROS generation, leading to parasite apoptosis without triggering host cell necrosis. Their safety profiles, along with synthetic accessibility, support further preclinical development (Fonseca-Silva *et al.*, 2011).

DNA Synthesis Inhibitor: Marinopyrrole A

Marinopyrrole A, an aromatic heterocycle from *Streptomyces* sp., inhibits *T. gondii* tachyzoites with an IC_{50} of 0.31 μM by intercalating into DNA and stalling replication forks. However, serum binding (>20%) reduces efficacy, indicating the need for optimized formulation or analog development. This pharmacokinetic limitation is being addressed through nanoparticle encapsulation strategies (Guo *et al.*, 2024; Martens *et al.*, 2022).

Protease Inhibitors: Gallinamide A and Related Lipodepsipeptides

Gallinamide A, isolated from *Schizothrix* and *Symploca* cyanobacteria, exhibits targeted inhibition of falcipain and cruzain cysteine proteases. It demonstrates efficacy against *P. falciparum* (IC_{50} ≈ 8.4 μM) and *L. donovani* (~9.3 μM), although it is inactive against *T. cruzi*, likely due to lack of compound permeability or target engagement (Barbosa Da Silva *et al.*, 2022; Miller *et al.*, 2014). Gallinamide binds irreversibly to parasite cysteine proteases through its α, β-unsaturated carbonyl moiety, inducing proteolytic dysfunction and starvation (Boudreau *et al.*, 2019).

Cytoskeletal Disruptors: Oroidin and Analogues

Oroidin, a bromopyrrole alkaloid from *Agelas* sponges, displays moderate multi-protozoan activity (*P. falciparum, T. brucei, T. cruzi, L. donovani*) with IC_{50} ranging from 10-50 μM. It disrupts cytoskeletal integrity and mitochondrial morphology (Scala *et al.*, 2010). SAR studies show that halogenation and amide modifications enhance selectivity and potency, suggesting a promising scaffold for further lead optimization.

Marine Microbial Metabolites Against Anaerobic Protozoa

Anaerobic protozoa, including *Entamoeba histolytica, Giardia intestinalis*, and *Trichomonas vaginalis*, cause widespread gastrointestinal and urogenital infections, particularly in low-resource settings. Their unique metabolic adaptations such as reliance on fermentation, hydrogenosomes, and non-canonical redox enzymes offer distinctive drug targets. Marine-derived microbial compounds, particularly glycolipids and non-ribosomal peptides, have shown activity through mechanisms involving oxidative stress, transcriptional suppression, and cytoskeletal collapse (Priya *et al.*, 2008; Sabatke *et al.*, 2021).

Glycolipid-Mediated Membrane Disruption: Sulfoquinovosyldiacylglycerols (SQDGs)

SQDGs, primarily isolated from the brown alga *Lobophora variegata* but associated with epiphytic microbial consortia, exhibit potent *in vitro* activity (1-5 μg/mL crude extracts) against *Giardia, Entamoeba*, and *Trichomonas*. These sulfonated glycolipids incorporate into parasite membranes, inducing oxidative membrane damage and lytic death. The palmitoyl myristoyl variant shows the highest potency, and liposomal formulations are under exploration to enhance delivery and specificity (Estrella-Parra *et al.*, 2022; Kini *et al.*, 2020).

Transcriptional and Proteasomal Inhibitors: Tirandamycins and Carmaphycins

Tirandamycin B, a tetrahydrofuran-containing polyketide from *Streptomyces* spp., inhibits parasite RNA polymerases, impairing gene expression in anaerobic protozoa (Reusser, 1970). Similarly, carmaphycin B, a β-lactone containing peptide from marine cyanobacteria, disrupts proteasomal function. Although IC_{50} values for anaerobic protozoa remain limited in literature, mechanistic studies confirm host-independent targeting of conserved parasite machinery. Resistance profiling is needed to fully determine therapeutic viability (A. R. Pereira *et al.*, 2012).

Actin-Binding Peptides: Jasplakinolide, Symplocamide A, and Venturamides

Depsipeptides such as jasplakinolide (from *Jaspis* sp.), symplocamide A, and venturamides target cytoskeletal actin filaments, causing impaired motility, division, and encystation in anaerobic parasites. Jasplakinolide stabilizes F-actin, leading to morphological disarray and inhibition of phagocytosis in *Entamoeba histolytica*. These mechanisms are relevant across multiple protozoan genera, and although cytotoxicity must be carefully managed, analog development may allow improved selectivity (Bubb *et al.*, 1994; Posey & Bierer, 1999).

Marine Microbial Metabolites Targeting Helminths (Trematodes and Other Endoparasites)

Helminthic infections particularly those caused by *Schistosoma* species, affect over 200 million people worldwide and contribute to significant morbidity, especially in tropical and subtropical regions. Current treatments rely heavily on praziquantel and albendazole, both of which face emerging resistance and fail to target larval or migratory stages (Utzinger & Keiser, 2004). Marine-derived microbial metabolites offer novel structural templates and mechanisms to combat helminthic infections, with some already showing efficacy in disrupting egg-laying, reproductive organ function, or tegument integrity of helminths (König *et al.*, 2006).

Naphthacene Glycosides: SF2446A2 from Marine *Streptomyces*

SF2446A2 is a naphthacene glycoside isolated from *Streptomyces* sp. derived from Mediterranean sponges. It demonstrates potent phenotypic activity against adult *Schistosoma mansoni*. At a concentration of 50 μM, SF2446A2 completely abolished egg-laying within 72 hours in ex vivo assays and induced severe tegumental damage, gonadal degeneration, and disorganization of oogenesis and spermatogenesis (Reimer *et al.*, 2015).

Histological evaluation of treated worms revealed vacuolation of gonadal tissues, erosion of the syncytial tegument, and disruption of musculature, effects not typically observed with praziquantel. The compound likely acts on nuclear or mitochondrial DNA replication pathways or through oxidative stress induction, although the precise molecular mechanism remains to be fully elucidated (Winkelmann *et al*., 2021).

Multitarget Nucleoside Analog: Tubercidin as a Dual Anti-Protozoal and Anti-Helminthic Agent

Although primarily characterized as an anti-protozoal agent, tubercidin a nucleoside analog produced by *Streptomyces* and marine sponge symbionts has shown significant cross-activity against helminths. In murine models of *S. mansoni* infection, tubercidin treatment resulted in parasite clearance and reversal of hepatosplenomegaly, suggesting systemic efficacy. The compound likely inhibits DNA and RNA synthesis in schistosomes via its incorporation into nucleic acid chains, ultimately leading to parasite apoptosis. Moreover, *in vivo* tolerability studies demonstrated acceptable host safety, though caution is warranted due to its narrow therapeutic index. Its dual action across multiple parasitic phyla underscores its potential as a lead for developing broad-spectrum antiparasitic agents, particularly in co-endemic settings (Biabani *et al*., 2002; Pimentel-Elardo *et al*., 2010).

Perspective: Marine Actinomycete and Cyanobacterial Libraries for Anti-Helminth Discovery

The activity of tubercidin against *S. mansoni* opens the door to systematic screening of marine actinomycete and cyanobacterial metabolite libraries for anti-helminthic candidates. Genome mining of *Salinispora, Micromonospora*, and *Nocardiopsis* strains has revealed numerous biosynthetic gene clusters (BGCs) encoding PKS-NRPS hybrids, which may yield analogs capable of targeting schistosome tegument integrity, neuromuscular transmission, or reproductive processes. Furthermore, cyanobacterial depsipeptides and indole alkaloids known to modulate actin cytoskeleton or proteasome function in protozoa may show cross-activity against helminths due to conserved cellular machinery. Such structural scaffolds have yet to be systematically tested in *Schistosoma, Brugia*, or *Echinococcus* models, representing a major knowledge gap and an opportunity for future exploration. Table 1 describes a comparison of various marine metabolite's sources, targets, efficacy, and selectivity, and Figure 1 depicts the comparison potency between some marine microbial antiparasitic metabolites.

MAJOR MARINEDERIVED MICROBIAL METABOLITES WITH ANTIPARASITIC POTENTIAL

Marine-derived microorganisms, particularly those associated with sponges, sediments, and cyanobacteria, have emerged as prolific sources of structurally diverse and pharmacologically potent natural products. Several of these microbial metabolites have demonstrated significant anti-parasitic activities against a broad range of protozoan parasites including *Plasmodium* spp., *Leishmania* spp., *Trypanosoma spp.*, and *Toxoplasma gondii*. Figure 2 depicts the chemical structures of major marine derived metabolites. These compounds span multiple phytochemical categories such as alkaloids, polyketides, macrolides, lipodepsipeptides, and β-lactones, each exhibiting unique structural scaffolds and mechanisms of action. Despite promising *in vitro* and some *in vivo* results, many of these metabolites remain underexplored in terms of pharmacokinetics, toxicity, and translational viability. The following Table 2 categorizes these compounds based on their phytochemical class, microbial source, parasitic target, and key pharmacological activities.

PHYTOCHEMISTRY AND STRUCTURAL DIVERSITY

In recent years, marinederived microbial sources, especially sponge-associated microorganisms, sedimentderived actinomycetes, and cyanobacteria (e.g. *Calothrix, Streptomyces, Salinispora, Moorea*), have become increasingly recognized as fertile reservoirs for structurally diverse antiparasitic metabolites. Isolation typically begins with collection of marine sponges or sediments, followed by stringent pretreatment protocols (e.g. dry heat, freezethaw, selective antibiotic pretreatment) and highthroughput cultivation using media optimized with seawater, specific carbon sources, and inhibitors to suppress fast-growing contaminants, facilitating recovery of rare genera such as *Salinispora* and marine *Streptomyces* spp (J. Chen *et al*., 2021; J. Kuo *et al*., 2019; Shrestha *et al*., 2021). From these biosources, diverse compound classes have emerged. *Salinispora tropica* and *S. arenicola* yield halogenated γlactamβlactone bicyclic compounds such as salinosporamide A (marizomib), produced via a hybrid PKSNRPS gene cluster featuring an irondependent halogenase responsible for chlorination of an unactivated methyl precursor. Likewise, *Streptomyces* species associated with sponges (e.g. *S. tateyamensis, S. marinus*) deliver alkaloids (tubercidin), polyketides (tirandamycin B), angucyclinones, glutarimides, and glycosylated polyenes with antiparasitic or enzyme inhibitory activity (Bauman *et al*., 2022; Gulder & Moore, 2010).

Biosynthetic Gene Clusters and Isolation Strategies

Environmental sampling of sponges, sediments, or cyanobacterial mats is followed by selective cultivation and genomic screening for PKS/NRPS gene clusters (Agrawal *et al*., 2017). For example, in *Salinispora* sp., gene architecture comprises a PKS module synthesizing polyketide backbone, an NRPS module incorporating the amino acid βhydroxycyclohexenylalanine, and a nonheme iron halogenase that installs the chlorine in salinosporamide A (Rocha-Martin *et al*., 2014). Similarly, gene clusters encoding cyclomarin in *Salinispora* spp. combine NRPS modules with unusual tailoring domains to produce a cyclic peptide scaffold.

Table 1: List of Marine-Derived Microbial Antiparasitic Metabolites.

Compound	Source Organism	Target Parasite(s)	*In vitro* Potency (IC_{50}/EC_{50})	Host Cytotoxicity/ SI	Proposed Mechanism of Action	References
Valinomycin	*Streptomyces* sp. from marine sponge	*T. brucei, L. major*	3.2 nM (*T. brucei*), <110 nM (*L. major*)	CC_{50} >10 µM; SI >100	Ionophore disrupting K^+ homeostasis in protozoa	(Pimentel-Elardo *et al.*, 2010)
Staurosporine	Marine *Streptomyces*	*T. brucei*	5.3 µM	Moderate cytotoxicity	Protein kinase inhibition	(Cartuche *et al.*, 2019; Choi *et al.*, 2024)
Tubercidin	Marine sponge symbiont	*T. cruzi, L. donovani, S. mansoni*	0.06-0.30 µM	Good tolerability in mice	Purine analog-nucleoside metabolism inhibition	(Choi *et al.*, 2024; Orhan *et al.*, 2010)
Renieramycin A	Marine sponge (*Xestospongia*)	*L. amazonensis*	~0.2 µg/mL	Low cytotoxicity	Mitochondrial dysfunction	(Halim *et al.*, 2011)
Marinopyrrole A	Marine *Streptomyces*	*T. gondii*	0.31 µM	IC_{50} ↑ in serum >20%	DNA synthesis inhibition	(Martens *et al.*, 2022)
Gallinamide A	*Schizothrix* / *Symploca* (cyanobacteria)	*P. falciparum, L. donovani*	8.4 µM (*Pf*), 9.3 µM (*Ld*)	Minimal cytotoxicity	Irreversible cathepsin L inhibition	(Tan & Salleh, 2024)
Oroidin	Sponge (*Agelas* spp.)	*P. falciparum, T. brucei, L. donovani*	10-50 µM	Low-moderate toxicity	Cytoskeletal disruption	(Gribble, 2015; Mayer *et al.*, 2019)
SQDG lipids	Brown alga *Lobophora variegata*	*Entamoeba, Giardia, Trichomonas*	1-5 µg/mL (crude), pure not defined	Not reported	Membrane perturbation, oxidative stress induction	(Cantillo-Ciau *et al.*, 2010)
SF2446A2	Marine *Streptomyces*	*S. mansoni*	Functional inhibition (50 µM)	No major host toxicity noted	Tegumental and gonadal tissue degeneration	(Cantillo-Ciau *et al.*, 2010; Reimer *et al.*, 2015)

Mapping these BGCs allows prediction of structural modification and tailoring enzymes that drive halogenation, glycosylation, or macrocyclization (Pimentel-Elardo *et al.*, 2012). Figure 3 depicts the biosynthetic gene clusters for Salinosporamide and Cyclomarin.

Structural Diversity and Unique Motifs

Marine microbial metabolites display notable structural uniqueness; Halogenated scaffolds, such as salinosporamide A, featuring a chlorinated bicyclic γlactamβlactone core. Enediyne and polyene motifs, as seen in angucyclinones or tirandamycin derivatives (Wang *et al.*, 2021). Cyclic peptides and depsipeptides, exemplified by cyclomarin, lyngbyabellins, and analogues like homiamides (depsipeptides from *Streptomyces* ROA065). Glycolipid headgroups, including glycosidic sphingolipids from cyanobacteria and sponge symbionts, some of which display anti*Giardia* effect (though not detailed here) and possess unique βglycoside linkages (Moore, 1996). Structural features are often correlated with bioactivity; for example, the halogen substitution in salinosporamide analogues significantly enhances proteasome inhibitory potency, while removal or alteration of the halogen diminishes target affinity.

Structure Activity Relationships (SAR) Insights

Salinosporamide analogues (B-J, bromosalinosporamide, thioester derivatives)

Modifications at the halogen-bearing carbon or alkyl branch yield analogues with altered proteasome inhibition profiles. Retention of the bicyclic core structure with chlorine increases potency, whereas substitution often reduces selectivity index (Potts & Lam, 2010).

Lyngbyabellin analogues from cyanobacterial peptides

Variations in side chain length and cyclization status (macrocycle vs depsiforms) influence cytotoxicity and target selectivity,

implying fine structural tuning can enhance parasite selectivity (Fathoni *et al.*, 2020; Yokokawa *et al.*, 2001).

Depsipeptides like homiamides A-C

Changes in amino acid sequence or hydroxylation pattern influence antibacterial activity and cytotoxicity moderately but may indicate how to engineer antiparasitic efficacy (Kim *et al.*, 2024).

Tirandamycin B vs A

The keto-enol positional isomerism dramatically affects inhibitory activity against *Brugia malayi* AsntRNA synthetase; B (1keto4′enol) is active (IC_{50} ≈ 30 µM), whereas A shows different bacterial enzyme targeting and less antiparasitic activity (Pang *et al.*, 2021; Zhao *et al.*, 2014).

Table 3 describes that structural features and SAR of various marine-derived microbial metabolites with antiparasitic potential, and Figure 4 depicts the structure and SAR of Analog modifications of those marine microbial metabolites.

PHARMACOLOGY AND MECHANISM OF ACTION

In vitro Efficacy

Marinederived microbial metabolites such as salinosporamide A (marizomib) and gallinamide A, as well as manzamine A, have demonstrated promising inhibitory activity against parasitic protozoa in culture systems. Salinosporamide A, isolated from *Salinispora tropica*, exhibits potent activity against erythrocytic *Plasmodium falciparum* (H.-S. Lee & Jeong, 2020). A study reported IC_{50} in the low-nanomolar range, with comparative assays showing similar potency to proteasome inhibitor MG132 (IC_{50} ≈ 40 nM) during SYBR Green growth assays (Barzkar *et al.*, 2024; Prudhomme *et al.*, 2008), (Fan *et al.*, 2011). Cytotoxicity in host cells (mammalian) was minimal at these concentrations, yielding favorable selectivity indices (SI not explicitly quantified but inferred based on comparative MG132 data). Gallinamide A, a cyanobacterial depsipeptide, exhibited selective inhibition of *P. falciparum* W2 chloroquineresistant strain with IC_{50} ≈ 8.4 µM, and activity against *Leishmania donovani* (IC_{50} ~9.3 µM), with moderately low mammalian TC_{50} (≈ 10.4 µM), yielding SI around ~1.2 (Alvarez-Sánchez *et al.*, 2024). Manzamine A, a spongederived alkaloid, showed ~70 % inhibition of *Toxoplasma gondii* at approximately 0.1 µM in culture studies, implying IC_{50} in submicromolar range; cytotoxicity to host cells remained low at these doses (Rubio *et al.*, 2009). Comparative potency against drugresistant versus drugsensitive strains is emerging but limited. For example, salinosporamide A retains activity in *P. falciparum* strains resistant to conventional antimalarials, due to its mechanism targeting a conserved proteasome, rather than the usual drug transport or target mutations. This suggests minimal crossresistance with chloroquineresistant or artemisininresistant isolates (Rosenthal, 2023). Similarly, gallinamide A remains active against chloroquineresistant strain W2, highlighting its distinct mechanism via cysteine protease inhibition of falcipain homologues. Studies frequently report selectivity index (SI) as ratio of host cell TC_{50} to parasite IC_{50}; for gallinamide A the SI was below ideal (>10), but for salinosporamide A preliminary data suggest a significantly higher SI based on low cytotoxicity

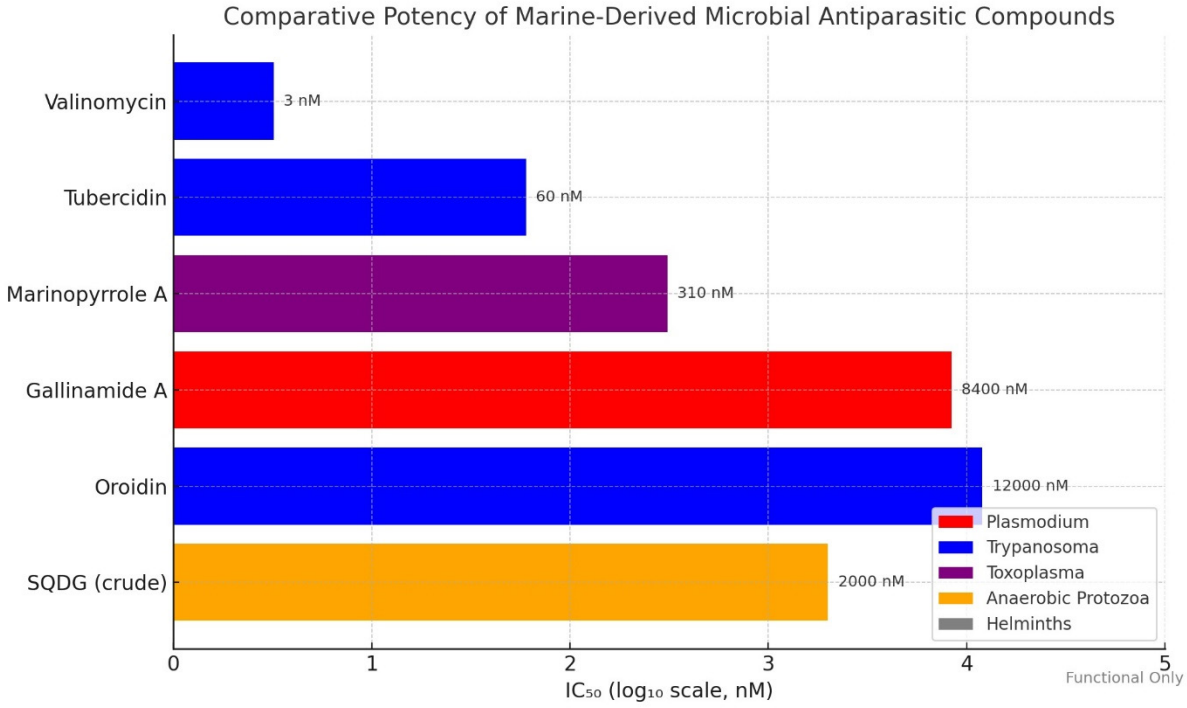

Figure 1: Comparative Potency of Key Marine-Derived Antiparasitic Compounds.

Table 2: Major MarineDerived Microbial Metabolites.

Phytoconstituent Class	Compound Name	Source	Parasite Target	Pharmacological Activity	References
βCarboline Alkaloids	Manzamine A; 8hydroxymanzamine; Manzamine F	Spongeassociated (Haliclona, Xestospongia etc.) microbial symbionts	*P. berghei* (rodent malaria) (nanomolar IC_{50}); also, *Leishmania, T. brucei*	Very potent antiplasmodial, induces morphological parasite damage	(El-Desoky & Tsukamoto, 2020; Kokkaliari *et al.*, 2021; Rao *et al.*, 2003)
Pyrrole / Imidazole / Indole Alkaloids	Calothrixin A, Calothrixin B; Oroidin (and analogues)	Marine cyanobacteria (e.g., *Calothrix, Lyngbya*)	P. falciparum, T. cruzi, T. brucei, L. donovani	Moderate-to-potent activity; oroidin analogues inhibit T. brucei rhodesiense etc.	(Rickards *et al.*, 1999; Xu *et al.*, 2016; Zidar *et al.*, 2014)
Macrolide / Cyclic Peptides	Cyclomarin A; Lyngbyabellin A; Salinipostins A	Marine actinomycetes (*Salinispora tropica, Lyngbya*, others)	*P. falciparum* (W2, D6, K1 strains)	Cyclomarin targets PfAp3Ase; salinipostins inhibit serine hydrolases; potent nanomolar activity	(Jensen *et al.*, 2015a, 2015b; Y. Lee *et al.*, 2017)
βLactone / Proteasome Inhibitors	Salinosporamide A (Marizomib) and analogues	*Salinispora tropica* and *S. arenicola*	*P. falciparum in vitro* antimalaria screens	Also, in oncological trials; mechanism proteasome inhibition	(Jensen *et al.*, 2015a; Sülzen *et al.*, 2025)
Lipodepsipeptides	Gallinamide A (Symplostatin4)	Marine cyanobacteria (*Schizothrix, Symploca*)	*P. falciparum* (IC_{50} ~8.4 μM), *L. donovani* (~9.3 μM)	Selective cysteine protease inhibitor (cathepsin/cruzain)	(Stolze *et al.*, 2012)
Glycosylated Polyketides / Siderophores	Actinosporin A	Spongeassociated Actinobacteria	*T. brucei* (antitrypanosomal)	Unique glycosylated scaffold; early-stage lead	(Gonçalves *et al.*, 2022; Selim *et al.*, 2021)
Nucleoside Analogue	Tubercidin (and derivatives e.g., 3′ deoxytubercidin)	Streptomyces spp., cyanobacteria, sponge symbionts	*T. cruzi* (antitrypanosomal), antiprotozoal	Potent antitrypanosomal; some derivatives show low host toxicity	(Nwoke *et al.*, 2024)

and nanomolar potency (Afonso *et al.*, 2023; Conroy *et al.*, 2014; Ettari *et al.*, 2021).

In vivo & Preclinical Activity

Salinosporamide A has advanced into animal infective models of malaria with notable efficacy. In a murine model using *P. yoelii*, Salinosporamide A, administered orally at ~130 μg/kg, significantly inhibited parasitemia and prolonged survival compared to untreated controls. This ultralow dose efficacy underscores exceptional potency and pharmacodynamic effect (Prudhomme *et al.*, 2008). Table 4 describes a comparative overview of *in vitro, in vivo* and mechanistic data of various microbial metabolites.

Mechanisms of Action

Proteasome Inhibition by Salinosporamide A

Salinosporamide A exerts its potent activity by irreversibly inhibiting the 20S proteasome in parasite cells. Structural studies reveal that the β-lactone moiety reacts with the nucleophilic Thr1 residue in the proteasome's catalytic site, forming a stable adduct and permanently disabling proteolytic activity. The adjacent γ-lactam ring and chlorine substituent facilitate precise orientation and internal cyclization, cementing the bond (Groll *et al.*, 2018; Potts & Lam, 2010). Biochemically, treatment with salinosporamide A results in accumulation of ubiquitinated proteins in *P. falciparum*, indicative of blocked protein turnover. This leads to cell cycle arrest at ring and schizont stages, inhibiting progression through DNA synthesis and schizogony, culminating in parasite death (Lindner *et al.*, 2013; Ponts *et al.*, 2011).

Cysteine Protease (Falcipain) Inhibition by Gallinamide A

Gallinamide A targets cysteine proteases, particularly falcipain enzymes in the malaria parasite, as well as Cathepsin L1 homologues. It binds irreversibly to the active-site cysteine residue, potently inhibiting enzymatic activity (IC_{50} ~17.6 pM against human Cathepsin L1) (Boudreau *et al.*, 2019; Miller *et al.*, 2014). In parasites, blockade of falcipain prevents hemoglobin

digestion within the food vacuole, starving the parasite of essential amino acids and disrupting cellular metabolism, leading to death (Pasupureddy *et al.*, 2019).

Membrane Disruption / Alternative Targets (e.g. Manzamines and Others)

Although the exact molecular targets of manzamine A remain incompletely characterized, its antiparasitic effect is attributed to perturbation of parasite membrane integrity, possible interference with calcium signaling or actin dynamics, and modulation of host immune responses. Its structure, a polycyclic alkaloid scaffold, likely intercalates into lipid bilayers or binds peripheral proteins, destabilizing parasite structural homeostasis at submicromolar concentrations (Hamann, 2007; Peng *et al.*, 2010). Figure 5 depicts the mechanisms of action of marine-derived compounds like Salinosporamide A, Gallinamide A, and Manzamines.

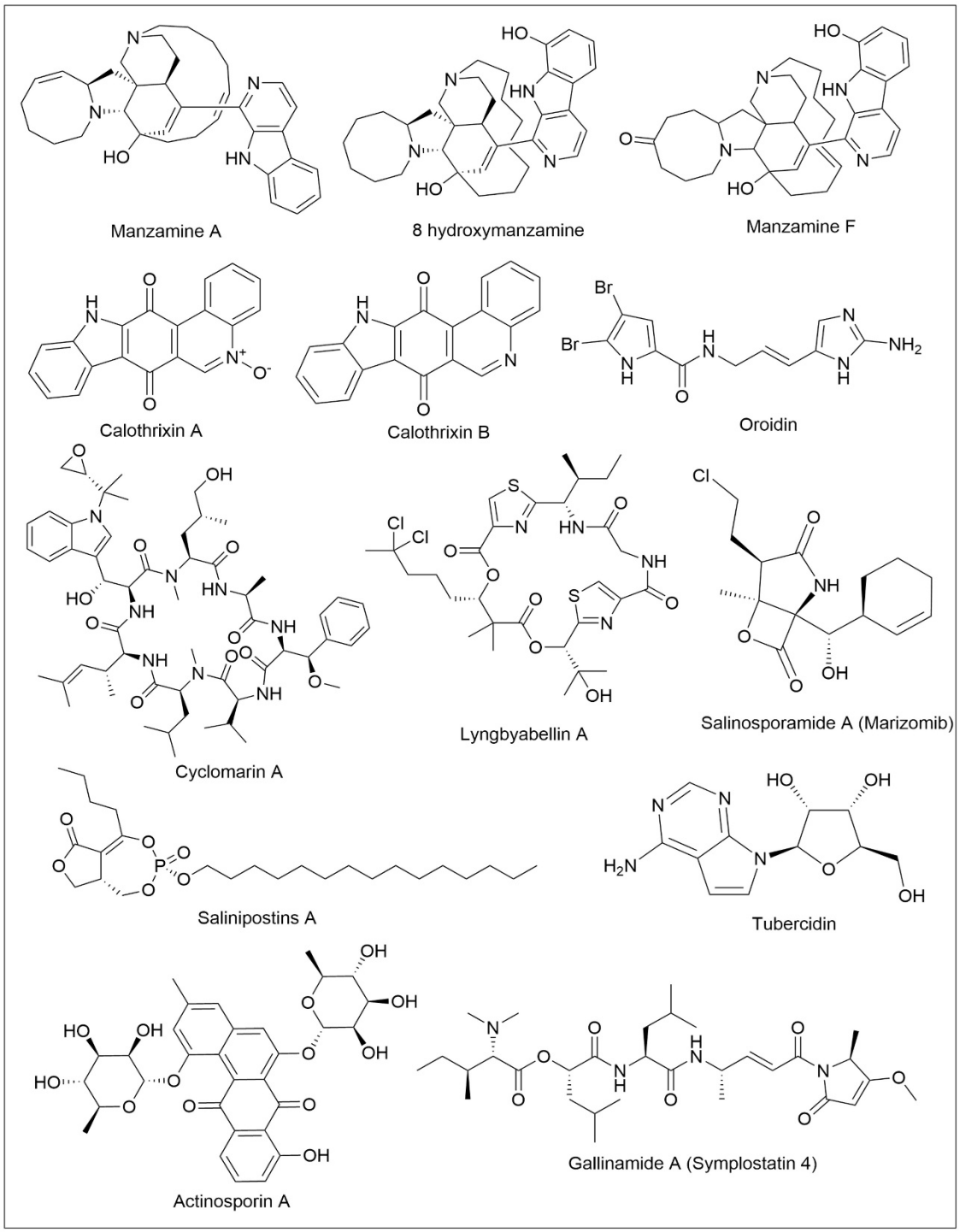

Figure 2: Chemical structures of representative compounds.

TOXICOLOGY, SAFETY & ADMET

Manzamine A demonstrates appreciable cytotoxicity in multiple mammalian cell types. In differentiated osteoclast progenitors, IC_{50} values of approximately 1.9-2.5 μM at 24-72 hr were observed, with dosedependent apoptosis confirmed via caspase3/7 assays. Similar potency (~2-3 μM) is consistent across preosteoblast and mature osteoblast lines in MTS assays. These values correspond roughly to ~0.7-2 μg/mL, indicating moderate host cell cytotoxicity at concentrations overlapping antiparasitic doses (manzamine A antimalarial IC_{50} typically submicromolar) (Maykovich *et al.*, 2024). In contrast, cyclomarin A exhibits substantially lower host cytotoxicity, as minimal inhibition of mammalian cells has been reported at concentrations effective against parasites though explicit CC_{50} values are less documented than for manzamine.

In vivo Tolerability & Adverse Effects

In murine *in vivo* antimalarial efficacy studies, manzamine A was used in Swiss albino mice at doses up to 100 μmol/kg (approximately 40-50 mg/kg depending on salt form) administered intraperitoneally or orally over one or two consecutive days. These regimens achieved >90% parasitemia reduction and ~40% survival at 60 days postinfection, with no overt signs of acute toxicity or organ pathology reported in primary study endpoints (Ang *et al.*, 2000; Laport *et al.*, 2009). A recent oncology xenograft study delivered 30 mg/kg manzamine A in tumorbearing mice for multiple weeks; body weight remained stable and serum liver enzymes were comparable between treated and control groups, indicating acceptable tolerability at this dosing level (Melfi *et al.*, 2023).

ADMET Properties

Solubility

Manzamine A is poorly watersoluble, often formulated as oil suspensions or with Tween for *in vivo* dosing; specific solubility metrics remain unreported (Palem *et al.*, 2017).

Metabolic stability & halflife

In vivo pharmacokinetic profiling in antimalarial studies revealed detectable plasma concentrations peaking at maximum 4 hr and persisting at quantifiable levels at 48 hr postinjection, suggesting slow clearance and long systemic exposure (Looareesuwan *et al.*, 2002; White, 2013).

Structure-derived liabilities

Analogue SAR studies (amidation at βcarboline positions) reduced cytotoxicity while retaining activity; for example, certain position8 amides dosed at 30 mg/kg orally suppressed parasitemia by ~62% with no apparent toxicity, suggesting that structural optimization can improve ADMET profiles (Karan *et al.*, 2020; Uddin *et al.*, 2020). For pentabromopseudilin, while highly potent *in vitro*, its high halogen content (>70% bromine) raises concerns regarding potential bioaccumulation, offtarget toxicity, and limited metabolic clearance (Bond *et al.*, 2013). Historical data indicate *in vitro* activity at submicromolar IC_{50}, but early therapeutic developments failed in animal studies and no modern ADMET or *in vivo* mammalian safety data are available (Janse van Rensburg *et al.*, 2023). Table 5 describes the summary of toxicity and ADMET properties of some marine microbial metabolites with anti-parasitic activity.

Table 3: Structural features and SAR highlights of selected marine-derived microbial metabolites with antiparasitic potential.

Compound	Key Structural Motif	SAR/Analog Modifications	Effect on Potency or Selectivity	References
Salinosporamide A/B/J	Halogenated γlactamβlactone bicyclic	Variation of halogen (Cl, Br), butyrate substitutions	ClA most potent; Br or nonhalogen lower activity	(Agarwal *et al.*, 2017; Sülzen *et al.*, 2025)
Cyclomarin analogues	Cyclic peptide scaffold	Tailoring side chains, ring size	Affects selectivity vs parasite proteasome	(Kazmaier & Junk, 2021; Ribeiro *et al.*, 2023)
Lyngbyabellins	Macrocyclic depsipeptide	Side chain hydroxylation, cyclodepsipeptide variants	Alters cytotoxicity/selectivity indices	(Alvarez-Sánchez *et al.*, 2024; Fathoni *et al.*, 2020)
Tirandamycin A vs B	Polyeneketone vs ketoenol	Isomerism between tautomeric forms	B active against parasite enzyme; A less so	(Jiang *et al.*, 2020)
Homiamides A-C	Linear/depsipeptide variants	Amino acid substitution, hydroxylation pattern	Modulates antimicrobial but unknown antiparasitic	(Kim *et al.*, 2024)

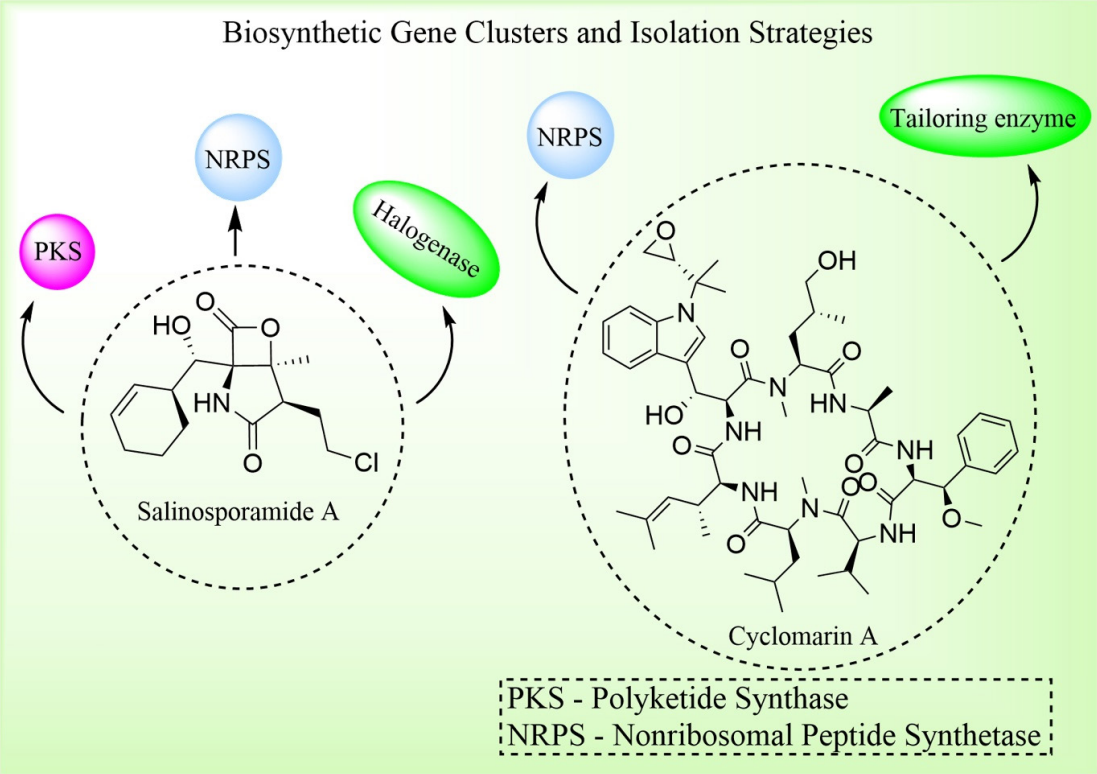

Figure 3: Biosynthetic gene clusters for Salinosporamide (PKS-NRPS with halogenase module) and for Cyclomarin (NRPS module with tailoring enzyme).

Table 4: Pharmacological comparative overview of *in vitro, in vivo* and mechanistic data for the key compounds.

Compound	Parasite(s)	*In vitro* IC_{50} (Selectivity Index)	*In vivo* Efficacy (Model, Dose)	Proposed Mechanism	References
Salinosporamide A	*P. falciparum* (sensitive/ resistant)	~40 nM; SI high (minimal host toxicity)	*P. yoelii* mice; 130 µg/kg orally → parasitemia suppressed	Irreversible 20S proteasome inhibitor; cell-cycle arrest	(Krishnan & Williamson, 2018)
Gallinamide A	*P. falciparum* W2 (resistant); *L. donovani*	~8.4 µM (SI ~1.2)	No *in vivo* data yet	Irreversible cysteine protease (falcipain) inhibitor	(Stoye *et al.*, 2019), (Siddiqui *et al.*, 2018)
Manzamine A	T. gondii	IC_{50} ~0.1 µM (~70 % inhibition); SI favorable	Not tested in animal infection models	Membrane disruption; actin/calcium interference	(Hamann, 2007)

FUTURE DIRECTIONS

Future efforts to translate marine-derived microbial metabolites into clinically relevant antiparasitic therapies must prioritize an integrated and multidisciplinary approach. The first imperative is to optimize compound accessibility through synthetic biology and metabolic engineering. Expression of biosynthetic gene clusters in heterologous hosts such as *Streptomyces, E. coli*, or *Saccharomyces cerevisiae*, coupled with promoter engineering and chassis optimization, can overcome the supply limitations of rare marine microbes. Equally important is the rational design of semi-synthetic analogues using medicinal chemistry and Structure-Activity Relationship (SAR) insights to improve pharmacokinetics, solubility, and target specificity while minimizing host cytotoxicity. In parallel, there is an urgent need for standardized *in vivo* validation pipelines. Most compounds currently lack robust preclinical studies across parasitic models. Establishing comparative efficacy data, toxicity thresholds, and therapeutic windows using murine models of malaria, leishmaniasis, and trypanosomiasis will provide foundational data required for IND-enabling studies. Moreover, collaborative screening platforms that pair phenotypic high-content assays

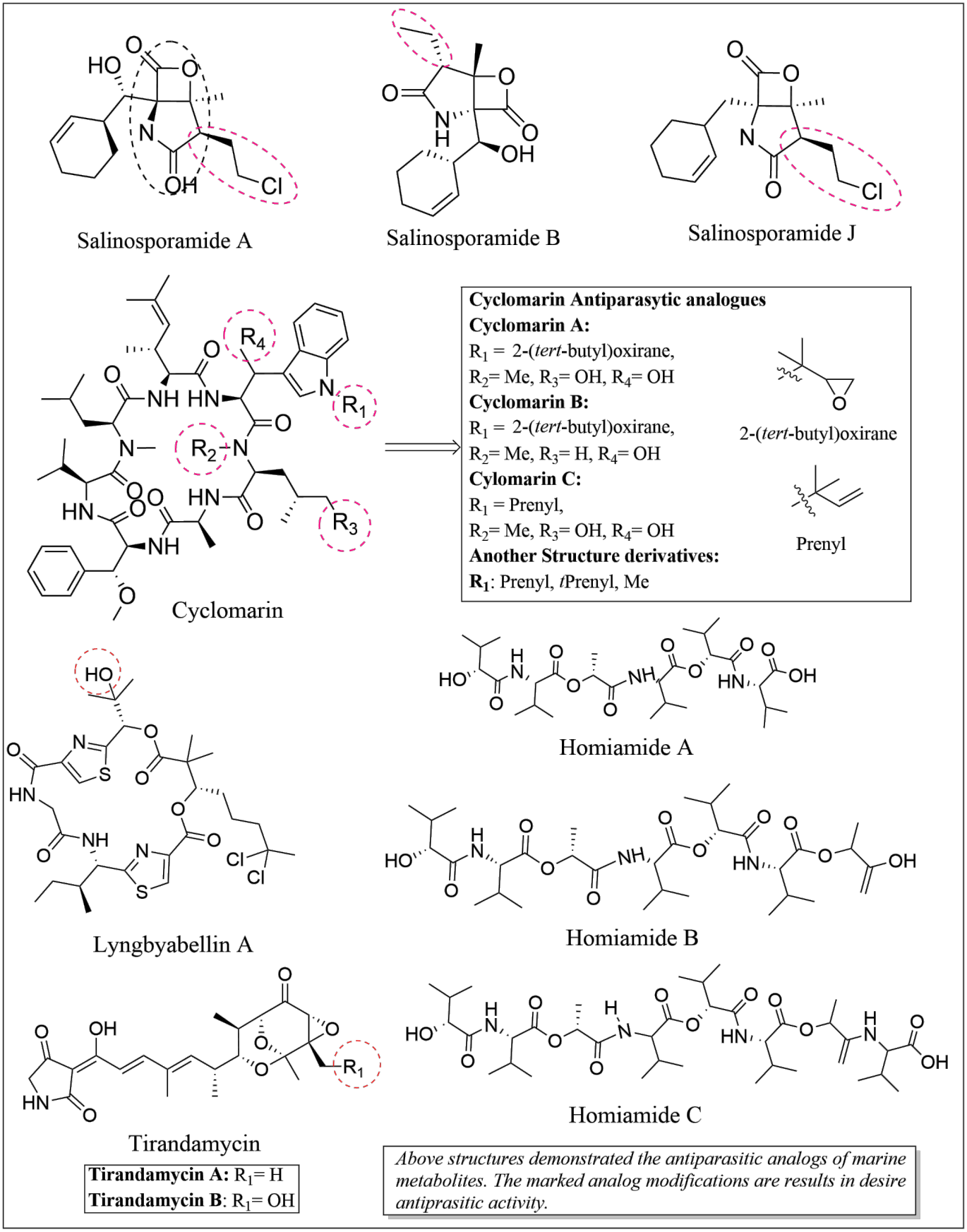

Figure 4: Structure and SAR of Analog modifications of marine microbial metabolites.

Table 5: Toxicity & ADMET properties of selected marine microbial metabolites with antiparasitic activity.

Compound	Cytotoxicity (CC_{50}/SI)	*In vivo* Toxicity Signs	ADMET Characteristics	References
Manzamine A	IC_{50} ~1.9-2.5 µM in mammalian cells; SI 2-10	Well tolerated up to ~50 mg/kg; stable weight, normal liver enzymes	Poor aqueous solubility; long halflife (~48 hr); plasma peak at 4 hr	(Ang *et al.*, 2000; Ashok *et al.*, 2015; Hamann, 2007)
Cyclomarin A	Minimal reported cytotoxicity; high selectivity	No published *in vivo* toxicity data	Likely favorable; low halogen load; limited data	(Taylor *et al.*, 2022; Vasudevan *et al.*, 2013)
Pentabromopseudilin	IC_{50} ~0.1 µM bacterial/mammalian; low SI	No modern *in vivo* data reported	Extremely halogenated; potential bioaccumulation, metabolic liability	(S. Chen & Li, 2025; D. T. F. Kuo *et al.*, 2022)

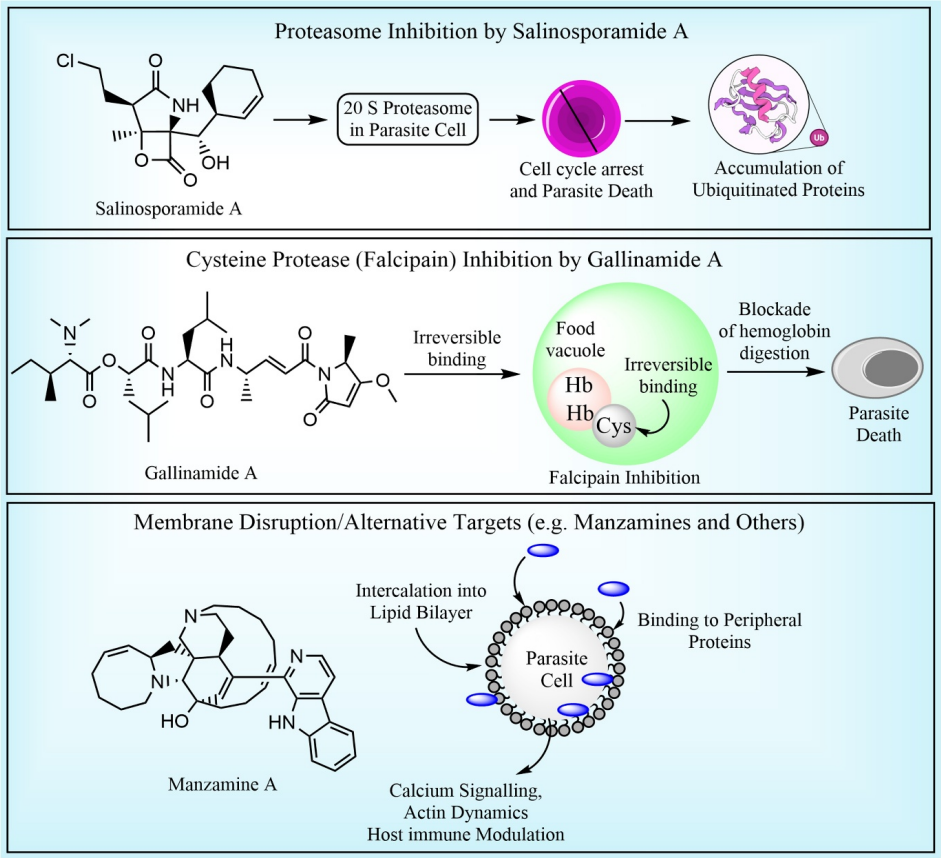

Figure 5: Mechanisms of action of some marine-derived compounds, shows their diverse molecular targets across key parasitic pathways.

with transcriptomics, proteomics, and chemical genomics will be critical for target deconvolution and resistance profiling. From a translational perspective, regulatory and environmental frameworks must also be proactively addressed. As marine resources fall under international conventions like the Nagoya Protocol, ensuring ethical bioprospecting, traceability, and benefit-sharing will be essential for sustainable drug development. Additionally, public-private partnerships should be fostered to de-risk early-phase development of marine microbial metabolites, particularly for neglected tropical diseases. Finally, the field would benefit from a global marine metabolite repository that integrates genomic, chemical, and pharmacological metadata, enabling data-driven prioritization and accelerating lead progression. By systematically overcoming these challenges, marine microbial metabolites can be repositioned from underutilized biological assets to next-generation antiparasitic therapies with broad global health impact.

CONCLUSION

Marine-derived microbial metabolites have emerged as a promising frontier in the discovery of novel anti-parasitic agents. Over the last two decades, scientific advancements in marine microbiology, natural product chemistry, and pharmacology have converged to uncover a wide array of structurally unique compounds with activity against protozoan and helminthic parasites. These include alkaloids, cyclic peptides, macrolides, lipodepsipeptides, and proteasome inhibitors, many of which exhibit submicromolar potency and high selectivity against key human parasites such as *Plasmodium falciparum, Leishmania donovani, Trypanosoma brucei*, and *Toxoplasma gondii*. Notable examples such as salinosporamide A, gallinamide A, and manzamine A have demonstrated mechanism-based activity targeting proteasomes, cysteine proteases, and cell membranes, respectively. Importantly, several of these agents show low cytotoxicity and promising therapeutic indices *in vitro*, with a few also validated in *in vivo* models. Despite this strong potential, the translational progress of these compounds remains limited. None have yet entered clinical trials for anti-parasitic indications, primarily due to challenges such as low natural abundance, difficult cultivation of marine microorganisms, biosynthetic complexity, and incomplete ADMET profiles. However, advances in genome mining, heterologous gene cluster expression, and semi-synthetic derivatization are beginning to resolve these barriers. The collective evidence compiled in this review highlights the underexplored but highly valuable space of marine microbial metabolites. They are poised to significantly expand the therapeutic toolkit for combating parasitic diseases, especially in the context of rising drug resistance and limited current options.

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ABBREVIATIONS

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity; **BGC:** Biosynthetic Gene Cluster; **CC50:** 50% Cytotoxic Concentration; **DNA:** Deoxyribonucleic Acid; **F-actin:** Filamentous Actin; **IC_{50}:** Half Maximal Inhibitory Concentration; **IND:** Investigational New Drug; **µM:** Micromolar; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of Activated B cells; **NRPS:** Non ribosomal Peptide Synthetase; **PBK:** Physiologically Based Kinetic; **Pf:** *Plasmodium falciparum*; **PKS:** Polyketide Synthase; **RNA:** Ribonucleic Acid; **SAR:** Structure Activity Relationship; **SI:** Selectivity Index; **SQDG:** Sulfoquinovosyldiacylglycerol; **TC_{50}:** 50% Toxic Concentration; **T. brucei:** *Trypanosoma brucei*; **T. cruzi:** *Trypanosoma cruzi.*

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Ishita Debnath, Suman Ghosh, Sumit Nandi, Soumik Bhattacharjee: Writing - original draft, Validation, Methodology, Conceptualization. **Avijit Ghosh, Samar Patra, Shubhajit Das, Disha Das, Piyush Mahato, & Bapan Khan:** Methodology, Formal analysis, Data curation. **Sajal Kumar Jha, Mithun Bhowmik, Amites Gangopadhyay, Rana Dutta-** Formal analysis, Data curation. **Jitendra Debata, Nirjhar Duttagupta, Sitansu Mondal, Ayantika Sil, Arindam Chatterjee, Sudip Roy & Nabanita Banik:** Study design, Methodology, Data curation.

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SUMMARY

Parasitic infections remain a pressing global health challenge, exacerbated by the emergence of drug resistance and limited efficacy of current therapies. Marine ecosystems harbor diverse microbial communities that produce structurally unique secondary metabolites with promising antiparasitic activity. This review provides a comprehensive synthesis of marine-derived microbial metabolites, highlighting their phytochemistry, pharmacological targets, toxicological evaluations, and translational potential. Particular emphasis is placed on structurally diverse compounds such as polyketides, alkaloids, peptides, glycolipids, and nucleoside analogues, which have demonstrated activity against parasites including *Plasmodium, Leishmania, Trypanosoma, Toxoplasma*, and *Schistosoma*. The manuscript also discusses selectivity indices, cytotoxicity studies, and emerging strategies such as synthetic biology, semi-synthetic derivatization, and advanced formulations to overcome scalability and bioavailability challenges. By bridging phytochemistry, pharmacology, and clinical prospects, this review underscores the untapped potential of marine-derived microbial metabolites as next-generation antiparasitic agents.

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