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Cortistatin and plakinamine steroidal alkaloids from the marine sponges of the genus *Corticium*: insights into their chemistry, pharmacology, pharmacokinetics and structure activity relationships (SARs)†

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Cortistatins and plakinamines represent a unique class of marine-derived steroidal alkaloids, renowned for their structural diversity and potent pharmacological activities. This review provides a comprehensive overview of their chemical characteristics, pharmacological profiles, pharmacokinetics, and drug-likeness properties, with a particular focus on structure–activity relationships (SARs). Indeed, we explored their distinct molecular architectures and classification within the broader family of marine alkaloids, highlighting key subclasses and derivatives identified through advanced analytical techniques. Their broad-spectrum bioactivities, including anticancer, anti-inflammatory, antimicrobial, and antiviral effects, are discussed in detail, supported by insights into SARs and pharmacophore identification that illuminate the molecular basis of their bioactivity. Additionally, we evaluate their pharmacokinetic attributes, including absorption, distribution, metabolism, and elimination (ADME), alongside their compliance with drug-likeness criteria, offering a holistic perspective on their potential for drug development.

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1. Introduction

Marine natural products (MNPs) represent a rich and prolific source of structurally unique bioactive compounds, many of which are at the forefront of drug discovery. The harsh and diverse conditions of marine ecosystems, including extreme temperatures, high pressures, salinity fluctuations, and varying light availability, drive the evolution of distinctive biochemical pathways in marine organisms, such as sponges, molluscs, corals, algae, and marine microorganisms.[1] These environmental pressures lead to the production of novel metabolites that exhibit potent and often highly selective bioactivity, making them compelling candidates for therapeutic applications.

Beyond their structural novelty, marine natural products are characterized by their ability to modulate unique molecular pathways, often targeting mechanisms that differ from those addressed by terrestrial compounds.[2] Marine-derived compounds demonstrate diverse bioactivities, including anticancer, anti-inflammatory, antimicrobial, and antiviral effects.[3,4] These activities are mediated through mechanisms such as the inhibition of cell proliferation, induction of apoptosis, and disruption of pathogenic biofilm formation. Moreover, the chemical diversity of these compounds offers opportunities to overcome drug resistance, a growing challenge in infectious disease and oncology.[5,6]

Several MNPs have successfully transitioned from the ocean to the clinic, demonstrating their therapeutic potential. *Trabectedin* (Yondelis®), derived from the tunicate *Ecteinascidia turbinate*, has been approved for treating soft tissue sarcoma and ovarian cancer.[7] Similarly, *Brentuximab vedotin* (Adcetris®) which incorporates the marine-derived dolastatin-10 is used to treat Hodgkin lymphoma. Another noteworthy example is

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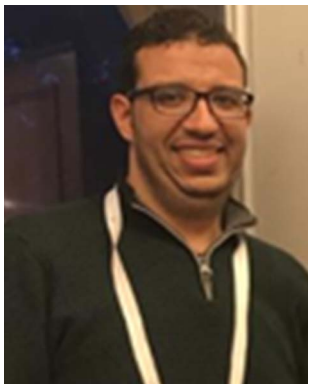
Ziconotide (Prialt®), a peptide isolated from the venom of the cone snail *Conus magus*, which serves as a potent non-opioid analgesic for severe chronic pain.[8] Beyond these, MNPs continue to constitute an invaluable rich source for antimicrobial agents, exemplified by compounds like salinosporamide A, the proteasome inhibitor from the marine bacterium *Salinispora tropica*, which has demonstrated promise as an anticancer agent.[9]

With the increasing demand for novel therapeutics, marine natural products (MNPs) remain a critical source of structurally diverse chemical scaffolds and lead compounds, reinforcing the significance of marine ecosystems as a reservoir for drug discovery. The ongoing exploration of marine environments remains crucial for expanding bioactive molecule libraries, uncovering new therapeutic targets, and addressing challenges like sustainable supply and synthesis complexities. Advances in chemical synthesis, aquaculture, and biotechnology continue to pave the way, enabling marine natural products to inspire new drug discoveries and provide unique mechanisms for treating complex diseases such as cancer and infectious diseases.

The marine sponge *Corticium*, is a genus within the phylum Porifera, found in coastal waters across various regions, notable for its distinctive encrusting growth form on underwater substrates. Like many sponges in nutrient-poor marine environments, *Corticium species* have evolved complex chemical defences, enabling them to deter predators, inhibit fouling organisms, and compete effectively within their ecological niche. These adaptations have led to the biosynthesis of an array of structurally diverse secondary metabolites, spanning several distinct classes, contributing to the sponge's resilience and ecological interactions including alkaloids, peptides, terpenoids, polyketides, and sterols.[10,11] Cortistatins are a class of steroidal alkaloids originally isolated from the marine sponge *Corticium simplex*. Their structure includes both a steroidal core and a rare pentacyclic scaffold, distinguishing them from other alkaloid classes. These compounds have gained attention in research for their unique structure and remarkable pharmacological potential, particularly their anticancer and anti-inflammatory properties. The primary bioactive compounds in this group, such as cortistatin A, have been studied for their selective inhibition of endothelial cell proliferation, which is essential in targeting angiogenesis in tumors.[12] This makes them potential candidates for anti-cancer therapies, especially in conditions where inhibiting blood vessel formation is advantageous. Further studies have shown that cortistatins may also possess antiviral, anti-inflammatory, and neuroprotective effects, broadening their potential therapeutic applications beyond oncology.[13–15]



Mohamed A. Tammam

Dr. Mohamed Tammam pursued his BSc degree in soil and water science in 2008 (Excellent with honors), at Fayoum University, Egypt where he received his MSc degree in biochemistry & chemistry of natural products in 2013, and later he received his PhD degree in Pharmacy (Excellent), from the National and Kapodistrian University of Athens (NKUA) focused on isolation and structure elucidation of secondary metabolites from marine organisms of the Red Sea under the joint mentorship of Prof. Vassilios Roussis and Prof. Efstathia Ioannou in 2020. After completing his PhD in Greece, he was promoted to an assistant professorship at the Biochemistry Department, Faculty of Agriculture Fayoum University, Egypt. Subsequently, since May 2021 till now, he has been conducting his first postdoctoral research focusing on isolation and structure elucidation of secondary metabolites from marine organisms, at the Section of Pharmacognosy and Chemistry of Natural Products, Department of Pharmacy, School of Health Sciences, (NKUA) with Prof. Vassilios Roussis and Prof. Efstathia Ioannou. His research interests cover bioactive natural products from marine macro- and microorganisms.

Adnane Aouidate

Dr. Adnane Aouidate completed his bachelor's degree in Organic Chemistry and Natural Products in 2009, where he received the Best Student Award, at the School of Sciences of Meknes, Moulay Ismail University in Morocco. He went on to earn his master's degree in molecular chemistry and chemistry of Natural Products in 2014, also receiving the Best Student Award, before obtaining his PhD in Computer-Aided Drug Design in 2019. His doctoral research, supported by an Excellent Scholarship from the Moroccan National Centre of Scientific and Technical Research, was conducted at the School of Sciences of Meknes, Moulay Ismail University (UMI). His work focused on employing 3D-QSAR, Molecular Docking, and ADMET techniques to investigate innovative strategies for drug discovery targeting protein kinases. Following the completion of his PhD in Morocco, Dr Aouidate held a postdoctoral position at the computer-Aided Drug Discovery Centre at the Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, from 2019 to 2020. He subsequently pursued a second postdoc with the Structural Bioinformatics and Cheminformatics Team at the Institute of Organic and Analytical Chemistry (ICOA) in Orleans, France, from 2021 until the end of 2022. In early 2023, he was appointed as an Assistant Professor at the School of Applied Sciences of Ait Melloul, Ibn Zohr University, Agadir, Morocco.

Among the other notable compounds produced by *Corticium* sponges are plakinamines, a group of nitrogen-containing alkaloids. Plakinamines are distinguished by their polycyclic, nitrogen-rich frameworks, which are not commonly found in terrestrial natural products. These complex structures are thought to play defensive roles in the marine environment, possibly deterring predators or microbial colonization.[16] From a pharmacological perspective, plakinamines have shown a range of biological activities, including significant antimalarial and cytotoxic effects. Their antimalarial potential has positioned them as candidates for developing treatments against malaria, especially as resistance to existing antimalarial drugs continues to rise.[17]

Steroidal alkaloids, including cortistatins and plakinamines, have garnered significant interest in drug discovery due to their unique structures and potent biological activities. The structural complexity of both classes of alkaloids poses some challenges for synthetic replication, which has driven researchers to develop novel synthetic strategies to produce these compounds in the lab.[18] While no commercial drugs have yet been directly developed from these specific marine alkaloids, their structural frameworks have inspired the design of drug candidates targeting cancer, inflammation, and infectious diseases.[19] For instance, cortistatins, isolated from marine sponges, exhibit exceptional anti-angiogenic activity by selectively inhibiting CDK8, a key regulator in cancer progression, making them valuable scaffolds for anticancer drug development.[20] Similarly, plakinamines, a class of polycyclic steroidal alkaloids, have demonstrated promising antimalarial and cytotoxic activities, suggesting their potential as templates for new therapeutic agents. The influence of steroidal alkaloids extends beyond marine-derived molecules, as seen in commercial drugs such as veratramine and cyclopamine, which target Hedgehog signalling pathways in cancer therapy.[21,22] These examples underscore the pharmaceutical relevance of steroidal alkaloids and highlight their potential as leads for next-generation therapeutics.

Building on our ongoing research into biologically active marine natural products,[23–30] the current review focuses on the detailed exploration of cortistatins and plakinamines, aiming to unlock their full therapeutic potential. By examining their chemistry, medicinal properties, pharmacokinetics, and drug-likeness, we seek to address critical knowledge gaps that currently limit their development as viable drug candidates. A particular emphasis is placed on investigating their pharmacokinetics, including bioavailability, metabolism, and safety profiles-key factors that determine the feasibility of translating these marine-derived compounds into effective and safe therapeutic agents. Through this focused approach, we aim to not only advance the understanding of these compounds but also provide a robust foundation for their future integration into drug development pipelines.

Manar M. Mahmoud

Manar Mohamed earned her BSc in Pharmaceutical Science (Excellent with Honors) from Helwan University, Egypt, in 2013. She completed her MSc in Pharmaceutical Science at the same institution in 2019, focusing on the "Isolation and Structure Identification of Bioactive Secondary Metabolites from Endophytic Microorganisms." During her MSc, she worked as a visiting student in 2016 at the Organic and Bioorganic Chemistry Department, Bielefeld University, Germany, where she gained hands-on experience in advanced techniques for natural product research. In May 2024, she completed her PhD in Natural Product Discovery at the Technical University of Denmark (DTU), supervised by Associate Professor Ling Ding, with a project titled "Omics-guided Bioactive Natural Products Discovery from Streptomyces." She has also gained international research experience as a visiting PhD student at the University of Hertfordshire in the UK, where she worked on computational drug discovery. Her expertise includes the isolation, purification, and structural elucidation of secondary metabolites using advanced chromatographic and spectroscopic techniques. Her research interests focus on bioactive natural products, particularly those derived from microbial sources.

Mariam I. Gamal El-Din

Dr. Mariam I. Gamal El-Din got her BSc in Pharmaceutical Sciences (excellent degree with honors) from the Faculty of Pharmacy, Ain Shams University, Cairo, Egypt (July 2008). She was awarded her M.Sc. degree (August 2013) and then her PhD degree (March 2021) in pharmaceutical sciences at the Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt. Mariam joined the Quadram institute as a visiting post-doc. scientist, at the Kroon Group in January 2023. She works on studying the effects of different polyphenols and plant extracts on the gut microbial metabolism and the associated health benefits accompanied with their consumption. She also works on extracting, fractionating, and metabolic profiling of polyphenol-rich extracts and isolating the bioactive constituents of promising extracts for further in-depth studies of their individual influence on gut microbial metabolism. During her scientific visit at Quadram Institute, she gained a lot of experience in the field of quantitative metabolomics and in vitro *colon model experiments. Her research interest is mainly focused on medicinal chemistry, food microbiome interactions, and plant metabolomics.*

2. Chemistry of steroidal alkaloids of the marine sponge of the genus *Corticium*

In this section, we will discuss systematically the chemical diversity of 36 marine derived steroidal alkaloids recorded from the marine sponge of the genus *Corticium*, which are listed in (Table 1 and Fig. 1–3), into three subgroups, in an ascending manner according to their publication date, as well as their isolation and structure elucidation.

2.1 Isolation and structure elucidation of B(9*a*)-homo-19-nor-steroidal alkaloids

Chemical examination of the chloroform crude extract of the Pacific marine sponge *Corticium* sp., which displayed a powerful cytotoxic effect towards KB cancer cell lines with 100% cytotoxicity led to the isolation of 3α-amino-23,29-imino-B(9*a*)-homo-19-nor-5α-stigmasta-1(10),7,9(11),23(N)-tetraene (**1**) and 3α-amino-23,29-imino-B(9*a*)-homo-19-nor-5α-stigmasta-l(10),7,23(N)-triene (**2**) (Fig. 1), compounds **1** and **2**, were found to be the first members of an unprecedent group of marine derived natural products with the unpredicted tetracyclic system in which 9,10 bond fission has occurred to yield a seven membered ring B. Indeed, the B(9*a*)-homo-19-nor- steroids were known only from terrestrial sources before the successful isolation of these two derived marine steroidal alkaloids. Compounds **1** and **2**, structures were elucidated through the extensive analysis of their 1D and 2D NMR data accompanied with the analysis of their HRMS spectra. Compounds **1** and **2**, were not examined for any relevant biological activity.[31]

Amr El-Demerdash

Dr. Amr El-Demerdash received his BSc degree (excellent with honors) in chemistry at the Faculty of Sciences, Mansoura University (Egypt) in 2004, and his MSc degree in organic chemistry (natural product chemistry) at the same university in 2009, before gaining his PhD in organic chemistry (discovery of pharmacologically active marine natural products and biomimetic total synthesis) from the prestigious French chemical institution CNRS-ICSN (Institute of Natural Products' Chemistry), University of Paris-Saclay (France), under the supervision of Dr Ali Al-Mourabit, in May 2016. After pursuing his PhD in France, Dr El-Demerdash was affiliated to Mansoura University (Egypt) as assistant professor while also conducting his first postdoctoral training (October 2017 to March 2019) within the fungal natural products chemistry group, CNRS/MNHN, Sorbonne Universities (France). Since April 2019 till now, Dr El-Demerdash has been conducting his second postdoctoral training, working on the biosynthesis of pharmacologically active plant natural products (Professor Anne Osbourn's group) at the John Innes Centre, Norwich Research Park, United Kingdom. Later, in December 2021, Dr El-Demerdash has been promoted to an Associate Professorship in organic and natural products chemistry, at Mansoura University, Egypt. Starting from August 2024, Dr El-Demerdash is embarking a new adventure as Assistant Professor in Chemical Biology at the school of Pharmacy, University of East Anglia, Norwich Research Park, Norwich-UK. Dr El-Demerdash's lab covers natural products chemistry-based drug discovery, encompassing various aspects including isolation and structure elucidation, small molecule development and bioinspired synthesis, and investigation of biosynthetic pathways.

2.2 Isolation and structure elucidation of cortistatins steroidal alkaloids

Due to its promising cytotoxic effect against HUVECs, in 2006, the methanolic extract of the marine sponge *C. simplex*, which was collected in Indonesia, from the Island of Flores was discovered by Aoki *et al.*,[12] through bioassay guided fractionation, which led to the first report of the unusual rearranged steroidal cortistatin core *i.e.*, cortistatins A (**3**), B (**4**), C (**5**), and D (**6**), (Fig. 2), their structures were formulated based on the by analysis of their high-resolution mass spectrometry (HRESI-TOF MS) data as well as the interpretation of their 1D and 2D NMR data, the relative configuration of the stereogenic centres of the obtained compounds were deduced based on the observed correlations in their NOESY spectra and the measured coupling constants between the protons of the stereogenic carbons, furthermore the proposed relative configuration of absolute configuration of cortistatin A (**3**), was confirmed through the analysis of its crystallographic data of its obtained crystals, additionally its absolute structure was further examined based on the observed data in its CD spectrum.

Due to the unique structure of cortistatins A–D (**3–6**), as well as their powerful cytotoxic effect, the same group of authors manage to isolate another four stigmastane-type steroidal alkaloids cortistatins derivatives namely cortistatins E (**7**), F (**8**), G (**9**) and H (**10**), (Fig. 2), from the same Indonesian marine sponge *C. simplex*, through the bioassay guided separation of its methanolic extract, their planar structures were deduced based on the observed correlation on their NMR spectra along with the analysis of their HR-ESI-MS spectra, furthermore their relative structure were designed based on the observed correlations in their NOESY spectra.[32]

Another and last successful trial for the isolation of this unusual steroidal alkaloids was done in 2007, Aoki *et al.*, from the Indonesian marine sponge *C. simplex*, based on the bioassay guided separation, which led to the isolation of three androstane-type steroidal alkaloids, namely cortistatins J (**11**), K (**12**), and L (**13**), (Fig. 2), their structures were determined through extensive analysis of their HRESI-TOFMS, 1D and 2D-NMR data, whilst the relative configuration of the asymmetric carbons of the isolated steroidal derivatives were deduced based on the observed correlations in their NOESY spectra, the absolute configuration of the stereogenic centres cortistatin J (**11**), was determined by circular dichroism (CD) exciton chirality

Table 1 List of 36 isolated steroidal alkaloids of the marine sponge *Corticium* sp. together with their displayed therapeutic activities

No	MF Name	Source	Biological activity Assay	Effect	Reference
B(9*a*)-homo-19-nor-steroidal alkaloids					
1	$C_{29}H_{44}N_2$ 3α-amino-23,29-imino-B(9*a*)-homo-19-nor-5α-stigmasta-1(10),7,9(11),23(N)-tetraene	*Corticium* sp.	Not determined for any relevant biological activity		31
2	$C_{29}H_{46}N_2$ 3α-amino-23,29-imino-B(9*a*)-homo-19-nor-5α-stigmasta-l(10),7,23(N)-triene	*Corticium* sp.	Not determined for any relevant biological activity		31
Cortistatins derivatives					
3	$C_{30}H_{36}N_2O_3$ Cortistatin A	*C. simplex*	Cytotoxicity	IC_{50} (0.0018 μM)	12
4	$C_{30}H_{36}N_2O_4$ Cortistatin B	*C. simplex*	Cytotoxicity	IC_{50} (1.1 μM)	12
5	$C_{30}H_{34}N_2O_4$ Cortistatin C	*C. simplex*	Cytotoxicity	IC_{50} (0.019 μM)	12
6	$C_{30}H_{34}N_2O_5$ Cortistatin D	*C. simplex*	Cytotoxicity	IC_{50} (0.15 μM)	12
7	$C_{32}H_{52}N_2O$ Cortistatin E	*C. simplex*	Cytotoxicity	IC_{50} (0.35–1.9 μM)	32
8	$C_{32}H_{50}N_2O$ Cortistatin F	*C. simplex*	Cytotoxicity	IC_{50} (0.35–1.9 μM)	32
9	$C_{31}H_{42}N_2O$ Cortistatin G	*C. simplex*	Cytotoxicity	IC_{50} (0.35–1.9 μM)	32
10	$C_{31}H_{44}N_2O$ Cortistatin H	*C. simplex*	Cytotoxicity	IC_{50} (0.35–1.9 μM)	32
11	$C_{30}H_{34}N_2O$ Cortistatin J	*C. simplex*	Cytotoxicity	IC_{50} (0.008 μM)	33
12	$C_{30}H_{36}N_2O$ Cortistatin K	*C. simplex*	Cytotoxicity	IC_{50} (0.04 μM)	33
13	$C_{30}H_{36}N_2O_2$ Cortistatin L	*C. simplex*	Cytotoxicity	IC_{50} (0.023 μM)	33
Plakinamine derivatives					
14	$C_{31}H_{50}N_2O$ Lokysterolamine A	*Corticium* sp.	Cytotoxicity Immunomodulatory Antibacterial Antifungal Nucleic acid cleaving	IC_{50} (0.5–5.0 μg mL^{-1}) Mild (0.13 and > 25.0) Inhibition zone (19.0 mm) Inhibition zone (9–11.0 mm) Inactive	34 and 35
15	$C_{31}H_{48}N_2O_2$ Lokysterolamine B	*Corticium* sp.	Cytotoxicity Immunomodulatory Antibacterial Antifungal	IC_{50} (0.5 – >2.0 μg mL^{-1}) Mild (0.0.48 and > 12.5) Inhibition zone (8.0 mm) Inhibition zone (0 mm)	34
16	$C_{33}H_{54}N_2O_2$ Plakinamine C	*Corticium* sp.	Cytotoxicity Anti-viral	IC_{50} (<3.2 μg mL^{-1}) Slight	16
17	$C_{33}H_{54}N_2O_2$ Plakinamine D	*Corticium* sp.	Cytotoxicity	IC_{50} (<3.3 μg mL^{-1})	16
18	$C_{32}H_{50}N_2O$ *N*,*N*-dimethyl-4-oxo-3-*epi*-plakinamine B	*Corticium* sp.	Cytotoxicity	IC_{50} (3.6 μg mL^{-1})	16 and 36
19	$C_{29}H_{48}N_2$ 24,25-Dihydroplakinamine A	*Corticium* sp.	Cytotoxicity Anti-viral	IC_{50} (5.7 μg mL^{-1}) Slight	16 and 36
20	$C_{30}H_{52}N_2$ —	*Corticium* sp.	Cytotoxicity Anti-viral	IC_{50} (4.9 μg mL^{-1}) Slight	16 and 36
21	$C_{31}H_{50}N_2O_2$ Plakinamine E	*Corticium* sp.	Cytotoxicity Antifungal Nucleic acid cleaving	IC_{50} (0.2 μg mL^{-1}) Inhibition zone (12.0 mm)	35
22	$C_{31}H_{48}N_2O$ Plakinamine F	*Corticium* sp.	Cytotoxicity Antifungal	IC_{50} (1.3 μg mL^{-1}) Inhibition zone (8.0 mm)	35

Table 1 (*Contd.*)

No	MF Name	Source	Biological activity Assay	Effect	Reference
			Nucleic acid cleaving	Inactive	
23	$C_{29}H_{44}N_2O$ Plakinamine G	*Corticium* sp.	Cytotoxicity	IC_{50} (6.8 μg mL^{-1})	36
24	$C_{31}H_{48}N_2O$ Plakinamine H	*Corticium* sp.	Cytotoxicity	IC_{50} (9.0–61.0 μg mL^{-1})	36
25	$C_{30}H_{48}N_2O$ 4α-hydroxydemethylplakinamine B	*Corticium* sp.	Cytotoxicity	IC_{50} (16.2–26.1 μg mL^{-1})	36
26	$C_{29}H_{50}N_2$ TEtrahydroplakinamine A	*Corticium* sp.	Cytotoxicity	IC_{50} (1.4 μg mL^{-1})	36
27	$C_{31}H_{50}N_2$ Plakinamine I	*C. niger*	Cytotoxicity	IC_{50} (2.52–11.27 μg mL^{-1})	37 and 40
28	$C_{30}H_{50}N_2$ Plakinamine J	*C. niger*	Cytotoxicity	IC_{50} (2.63–5.70 μg mL^{-1}) GI_{50} (2.4 μM)	37 and 40
29	$C_{32}H_{52}N_2O_2$ Plakinamine K	*C. niger*	Cytotoxicity	IC_{50} (0.698–2.48 μg mL^{-1})	37
30	$C_{32}H_{54}N_2O_2$ Dihydroplakinamine K	*C. niger*	Cytotoxicity	IC_{50} (0.697 μg mL^{-1})	37
31	$C_{32}H_{56}N_2O_2$ Plakinamine I	*Corticium* sp.	Cytotoxicity	IC_{50} (3.9 μg mL^{-1})	38
32	$C_{33}H_{52}N_2O_2$ 4-Acetoxy-plakinamine B	*Corticium* sp.	Enzyme inhibition	IC_{50} (3.75 ± 1.69 μM)	10
33	$C_{33}H_{58}N_2O$ Plakinamine L	*Corticium* sp.	Antibacterial	MIC (3.6 μg mL^{-1})	39 and 41
34	$C_{29}H_{48}N_2$ Plakinamine M	*Corticium* sp.	Antibacterial	MIC (15.8 μg mL^{-1})	39
35	$C_{33}H_{58}N_2$ Plakinamine N	*C. niger*	Cytotoxicity	GI_{50} (11.5 μM)	40
36	$C_{31}H_{50}N_2O_2$ Plakinamine O	*C. niger*	Cytotoxicity	GI_{50} (1.4 μM)	40

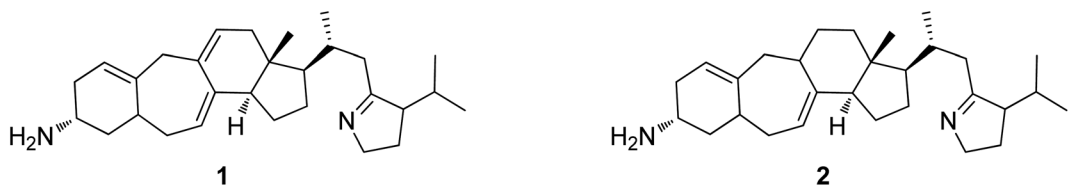


Fig. 1 Reported B(9*a*)-homo-19-nor- steroids **1** & **2**.

method, even though compounds cortistatins K (**12**), and L (**13**) didn't showed the expected split CD maxima in their CD spectra, but due to the high structural similarity of cortistatins rendered safe the assumption that both **12** and **13** share the same absolute configuration as that of cortistatins A (**3**), and J (**11**).[33]

2.3 Isolation and structure elucidation of plakinamines and related steroidal alkaloids

Chemical examination of the ethanolic extract of the marine sponge *Corticium* sp., collected in Indonesia from the island of Sulawesi, by scuba diving from a depth of −20 m, led to the isolation of two previously undescribed steroidal alkaloids, namely lokysterolamines A (**14**) and (**15**), (Fig. 3), their planar structures were elucidated through extensive analysis based on the collected data from the used spectroscopic method means *i.e.*, IR, HREIMS, and NMR spectroscopic methods. The relative configuration of the asymmetric carbons of compounds **14** and **15**, was prosed based of the obtained data from their NOE experiments along with the compression with the previously reported related analogue plakinamine A, isolated from the marine sponge *Plakina* sp.[34]

Bioassay guided separation of methanolic extract of the South Pacific marine sponge *Corticium* sp., collected from a depth of 12–18 m, at Porth Havannah, Vanuatu led to the isolation of five previously unreported steroidal alkaloids

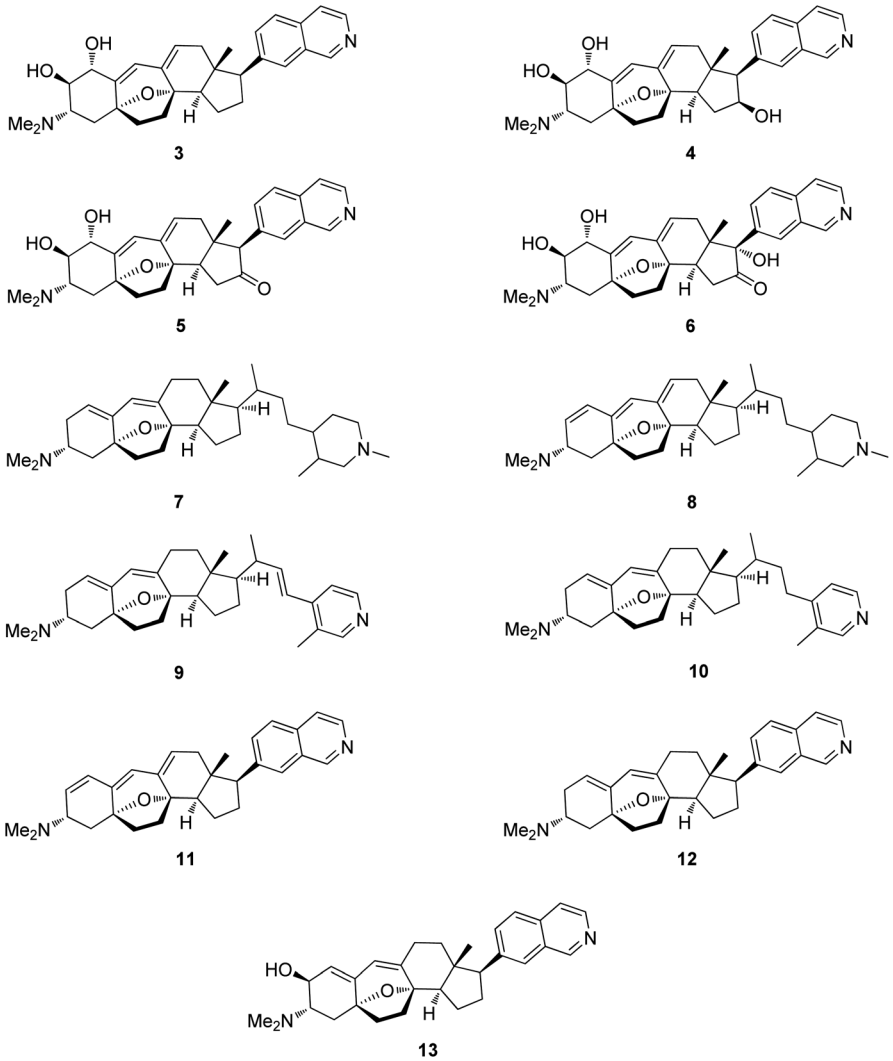


Fig. 2 Reported cortistatins **3–13**.

namely plakinamines C (**16**) and D (**17**), along with other three related compounds (**18–20**) (Fig. 3), their structures were elucidated through extensive analysis of their HREIMS, along with 1D and 2D NMR data. The relative configuration of the stereogenic carbons was assigned based on the analysis of the observed correlations in their ROESY spectra as well as with the compression with the previously reported related analogue plakinamine A, isolated from the marine sponge *Plakina* sp.[16]

Plakinamines E (**21**) and F (**22**), two previously un-described plakinamine related steroidal alkaloids along with the previously mentioned analogues lokysterolamine A (**14**) (Fig. 3), were isolated from the organic extract of the marine sponge *Corticium* sp., collected from the Harbor of Apra, Guam, at a depth of 5–15 m, where they were identified as *N*-oxo and 4-oxo derivative of the previously reported analogue lokysterolamine A (**14**), based on the interpretation of the observed correlation in their 1D and 2D NMR spectra accompanied with the obtained data from their HREIMS spectra.[35]

Borbone *et al.*, in their trial for the chemical examination of the second collection from the South Pacific marine sponge *C.* sp., were able to isolate in a pure form another four previously unreported steroidal alkaloids derivative namely plakinamines G (**23**), H (**24**), 4α-hydroxydemethylplakinamine B (**25**) and tetrahydroplakinamine A (**26**), together with the previously mention derivatives (**18–20**) (Fig. 3). Compounds **23–26**, planar structures were proposed based on the extensive analysis of their spectroscopic features *i.e.*, HREIMS, 1D and 2D NMR data, along with the comparison with the spectroscopic features of the previously reported analogues.[36]

Chemical examination of the methanolic extract Philippine sponge *C. niger*, collected from the island of Boracay, at a depth of 15–30 m, resulted in the isolation of the un-described plakinamines I (**27**), J (**28**), K (**29**), and dihydroplakinamine K (**30**), (Fig. 3). Compounds **27–30**, structures have been assumed based on the obtained data from the high-resolution mass measurements in combination with the extensive analysis of the observed correlations obtained from their 1D and 2D NMR spectra. Additionally, the relative configuration of the asymmetric carbons of compounds **27–30**, were deduced according to the acquired data from their NOESY and ROESY spectra.[37]

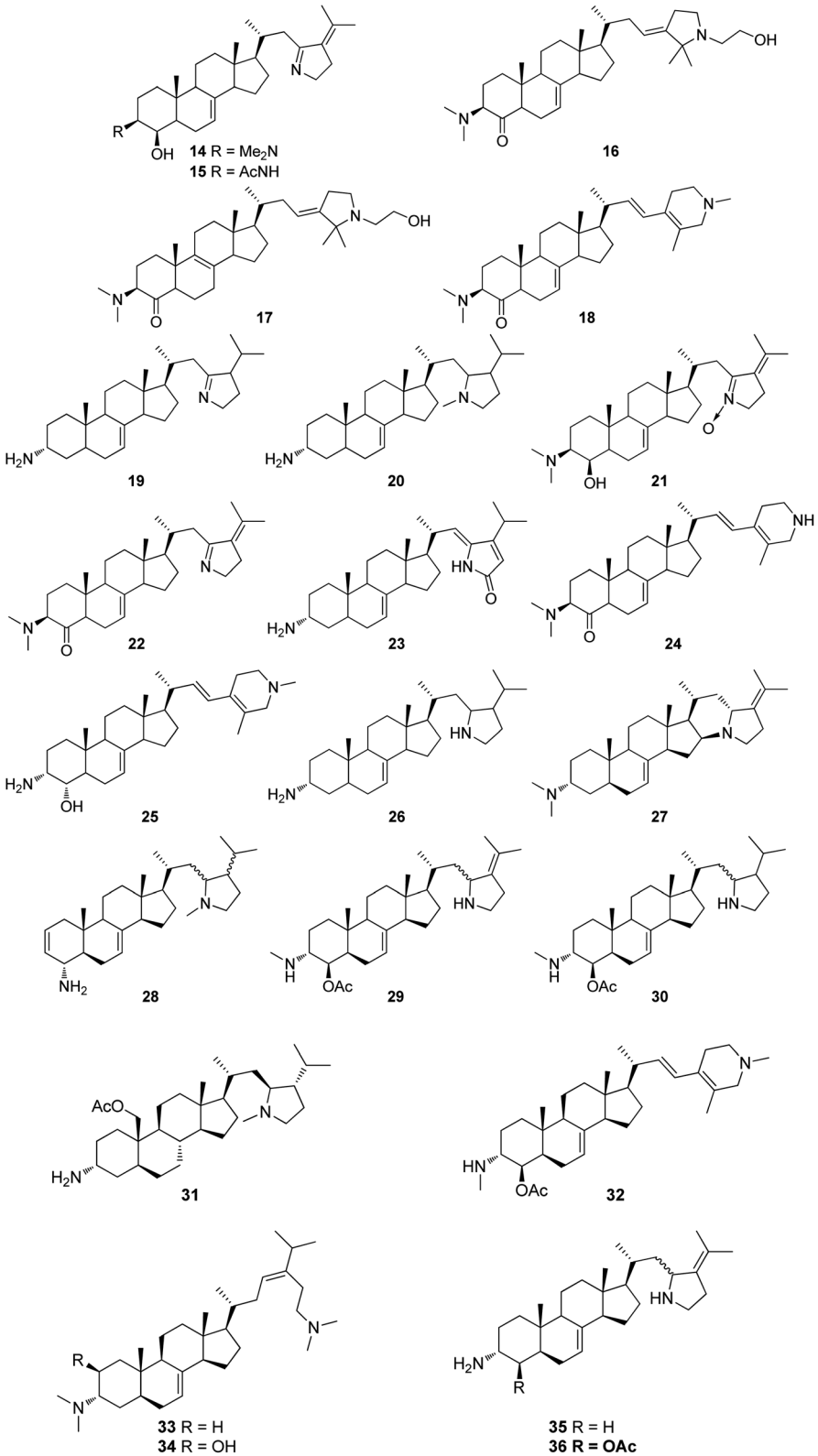


Fig. 3 Reported plakinamines 14–36.

Reinvestigation of the polar extract of the South Pacific marine sponge *Corticium* sp., by Zampella *et al.*,[38] resulted in the successful isolation of the naturally occurring 19-acetoxy-3α-amino steroid namely plakinamine I (**31**), (Fig. 3) for the first time, it is worth mention that even though it has the same name as that for compound (**27**), but they are two different structures.

Plakinamine I (**31**), planar structure was determined, through HRESIMS measurement as well as the interpretation of acquired NMR data accompanied with the obtained data from its chemical synthesis. Furthermore, the relative configuration of the stereogenic centres was deduced based on the observed correlation in its ROESY spectrum as well as the measured coupling constants.

4-Acetoxy-plakinamine B (**32**), (Fig. 3) another previously unreported stigmastane-type steroidal alkaloid, was isolated based on the bioassay guided separation, from the methanolic extract of the marine sponge *C.* sp., collected in the Province of Surat-Thani, at a depth of 18–30 m, based on the EIMS measurement, along with the extensive analysis of the obtained NMR data, its planar structure was deduced. Additionally, its relative configuration was proposed based on the analysis of the observed correlations of its NOESY spectrum and the measured coupling constants, along with the compression of the NMR data of similar and previously reported most steroids and triterpenoids. It is worth mention that 4-acetoxy-plakinamine B (**32**) represents the first example of the non-pregnane type steroid.[10]

Aknin *et al.*, reported the isolation of the first plakinamine derivative with acyclic side chain namely plakinamine L (**33**), from the organic extract of the south-west Madagascar marine sponge *C.* sp. Its planar structure was determined based on the analysis of their spectroscopic features *i.e.,* HREIMS, 1D and 2D NMR. Furthermore, the relative configuration of its stereogenic centres was determined by the interpretation of the observed correlation in its NOESY spectrum, as well as the comparison with the previously reported plakinamine A, isolated from the marine sponge *Plakina* sp.[10]

Further two acyclic side chain steroidal alkaloids included the previously mentioned plakinamine L (**33**) along with the previously unreported plakinamine M (**34**), (Fig. 3) were isolated from the methanolic extract of an unknown species of the marine sponge of the genus *Corticium*, through bioassay guided fractionation, compound plakinamine M (**34**) planar structure were assumed based on the obtained spectroscopic data including HRESIMS, 1D and 2D NMR data. Additionally, the relative configuration of the asymmetric centres was deduced based on the observed correlations in its NOESY spectrum as well as the measured coupling constants.[39]

Bioassay-guided fractionation of the polar extract of the Philippines marine sponge *C. niger*, collected at a depth of −15 to −20 m, from the west of Luzon, resulted in the isolation of two previously unreported plakinamines analogues, namely plakinamines N (**35**) and O (**36**), along with the previously mentioned plakinamines, I (**27**) and J (**28**) (Fig. 3). Compounds **35** and **36**, planar structures were determined based on the extensive analysis, of their 1D and 2D NMR data, along with their HRESIMS measurements, together with the comparison of their spectroscopic features with those of the previously reported analogues. The relative configuration of the asymmetric carbons of plakinamines N (**35**) and O (**36**), was assumed based on the analysis of their ROESY accompanied with the measured coupling constant along with the comparison of their ^{13}C spectra with those of the previously reported analogues.[40]

3. Pharmacological activities of steroidal alkaloids of the marine sponges of the genus *Corticium*

Steroidal alkaloids isolated from the marine sponge *Corticium* sp., were found to display a wide array of biological activities including cytotoxic, antimicrobial, anti-HIV, immunomodulatory, and nucleic acid cleaving activities.[16,34,35] Within this section we tried to highlight a shed on the different bioactivity's abilities of the marine sponge *Corticium* sp. steroidal alkaloids, as well as summarizing these biological abilities in Table 1.

3.1 Cytotoxicity

During the search of bioactive metabolites of marine origin, De Marino *et al.*, found that the crude extract of unidentified species of the marine sponge *Corticium*, showed a powerful cytotoxic effect against KB cancer cell line, with 100% cytotoxicity, even though the discovered promising cytotoxic effect of the crude extract, compounds **1** and **2**, that isolated from it, were not examined for any relevant biological activity.[31]

Aoki *et al.*, during their investigation of bioactive substances of marine origin, they examined the anti-proliferative effect of the MeOH extract of the Indonesia marine sponge *C. simplex*, against HUVECs where it displayed selective anti-proliferative effect, furthermore compounds cortistatins A–D (**3–6**), were found to be a strong cytotoxic effect against HUVECs cells with IC_{50} values of 0.0018, 1.1, 0.019, and 0.15 μM, respectively, and a selective index of 3300-fold for compound **3**, when compared to that of NHDF cells, and other cancer cells *i.e.,* KB3-1, K562, and Neuro2A cancer cell lines. Additionally, cortistatins A (**3**), displayed an inhibition effect towards the tubular formation and the migration of HUVECs induced by bFGF or VEGF at 2 nM concentration, respectively.[12] In contrast to cortistatins A (**3**), cortistatins E–H (**7–10**), displayed only weak anti-proliferative effect towards HUVECs with IC_{50} values ranged between 0.35 and 1.9 μM, and they didn't show any selectivity between HUVECs and other cell lines.[32]

Furthermore, cortistatin J (**11**) displayed anti-proliferative effect towards HUVECs cells with IC_{50} values of 0.008 μM, in contracts its $\Delta^{9,10}$ saturated derivative **12** and **13**, were found to be less cytotoxic with IC_{50} values of 0.04 and 0.023 μM, respectively.[33] Lokysterolamines A (**14**), and B (**15**) were examined for their cytotoxicity against P-388, A-549, HT-29, and MEL-28 tumour cell lines, where they were found to be strong anti-cancer agent with IC_{50} values of (0.5, 0.5, 1.0, and 5.0 μg mL^{-1}) and (1.0, 0.5, 1.0, and >2.0 μg mL^{-1}), respectively.[34]

Later after another successful trial by De Marino *et al.,* which led to the isolation of compounds **16–20**, where they were tested for their antitumour effect towards NSCLC-N6 (human bronchopulmonary non-small-cell lung carcinoma cells), and they displayed moderate cytotoxic effect with IC_{50} values of 3.2, <3.3, 3.6, 5.7, and 4.9 μg mL^{-1}, respectively.[16]

Furthermore, Lee *et al.*, examined the cytotoxic effect of the crude extract of the Guam marine sponge *Corticium* sp., where it showed moderate effect against K562 (human leukaemia cell

line), with IC_{50} value of 46 μg mL^{-1}, whilst compounds **14**, **21**, and **22**, obtained in their study, showed strong cytotoxic effect against the same examined cancer cell line with IC_{50} values of 0.9, 0.2, and 1.3 μg mL^{-1}, respectively.[35]

De Marino *et al.*, in their continuous efforts to discover bioactive ingredient from marine natural sources they examine compounds **23–26**, for their antitumour effect towards rat glioma (C6) and murine monocyte/macrophages (RAW 264) cell lines, while all of them were found to display cytotoxic effect against rat glioma (C6) with IC_{50} values of 6.8, 9.0, 26.1, and 1.4 μg mL^{-1}, respectively, only compounds **24** and **25**, showed cytotoxic effect against RAW 264 with IC_{50} values of 61.0 and 16.2 μg mL^{-1}, respectively.[36]

Additionally, the hydrochloride salts of **27**, **28**, and **30**, along with compound **29**, were tested for their cytotoxic activity against HCT-116 (human colon tumour cell line), where all of them displayed mild to potent effect against the examined cancer cell line with IC_{50} values of 4.99, 2.68, 0.697, and 0.698 μg mL^{-1}, respectively.[37]

Due to their promising cytotoxicity compounds **27–29**, were screened for their cytotoxicity against a panel of 11 tumour cell line in the Bristol-Myers Squib Pharmaceutical Research Institute, where compound **29** was the most potent (mean IC_{50}) 0.79 μg mL^{-1}, (max. IC_{50}/min. 2.48 μg mL^{-1}), while compound **27** exhibited the greatest selectivity (mean IC_{50}) 2.52 μg mL^{-1}, (max. IC_{50}/min = 11.27 μg mL^{-1}). Compound **28** also had significant cell panel results, with a mean IC_{50}, 2.63 μg mL^{-1} and max. IC_{50}/min. IC_{50} = 5.70 μg mL^{-1}.[37]

Plakinamine I (**31**) displayed good cytotoxic effect with IC_{50} value of 3.9 μg mL^{-1}, when it was examined for its cytotoxic effect against MCF7 cell lines.[38] Compounds **27**, **28**, **35**, and **36** were examined for their cytotoxic activity in the NCI- 60 anticancer screen, which includes a panel of seven human colon carcinoma cell lines (COLO 205, HCT-15, SW-620, HCC-2998, HT29, HCT-116, KM12), while compounds **28**, **35**, and **36**, displayed potent to moderate cytotoxic effect with GI_{50} values of 1.4, 11.5 and 2.4 μM, respectively, compound **27**, had only mild activity in the primer screening and was not further examined.[40]

3.2 Immunomodulatory

Lokysterolamines A (**14**), and B (**15**), showed moderate immunomodulatory activity (LcV/MLR > 187).[34]

3.3 Antimicrobial

Lokysterolamines A (**14**), and B (**15**), displayed antimicrobial effect against *B. subtilis* and *C. albicans*, with an inhibition zone of (19.0 and 11.0 mm) and (8.0 and 0 mm), respectively at a concentration of 50 μg per disc.[34] Moreover, Lee *et al.*, examined the antifungal activity of the crude extract of the Guam marine sponge *C.* sp., where it showed mild effect against *C. albicans*, with an inhibition zone of 6.5 mm using the disk paper method at a concentration of 25 μg per disk, whilst compounds **14**, **21**, and **22**, obtained in their study, at the same concentration displayed antifungal activity with a diameter of clear zones 9.0, 12.0, and 8.0 mm, respectively.[35] Additionally, Lu *et al.*, examined for the first time the ability of the plakinamines derivatives for *Mycobacterium tuberculosis* growth inhibition, where they found that compounds plakinamines L (**33**) and M (**34**), displayed a potent inhibition effect against *M. tuberculosis* with MIC values of 3.6 and 15.8 μg mL^{-1}, respectively. Moreover, both compounds were tested as well for their antibacterial effect against *S. aureus*, *B. subtilis* and *E. coli*, they were found to be inactive, also they were tested for their antifungal activity against *C. albicans*, where they showed weak effect at a concentration of 50 μg mL^{-1}.[39]

3.4 Antiviral

Compounds **16**, **19**, and **20**, showed slight anti-HIV effect, when examined against T leukaemia virus type one (HTLV-I), by checking the efficiency of the substrate to inhibit syncytia formation after HIV infection of an MT4 cell line.[16]

3.5 Nucleic acid cleavage

While compounds **14** and **22** were found to be in active when evaluated for their abilities to cleaved both double-stranded DNA and 16SrRNA isolated from *E. coli* at the concentration of 10 μg/20 mL in gel electrophoresis, compound **21** cleaved both nucleic acids totally using the same test.[35]

3.6 Enzyme inhibition

4-Acetoxy-plakinamine B (**32**), is the first steroidal alkaloid derived from marine source that displayed an inhibition effect toward acetylcholinesterase, where it showed a potent inhibition effect with IC_{50} value of 3.75 ± 1.69 μM, it is worth mention that among the best accepted models towards Alzheimer's disease (AD), treatments are the using of acetylcholinesterase (AChE) inhibitors.[10]

4. Structure activity relationships (SARs)

4.1 Cortistatins structure activity relationships

Cortistatins are classified into three types based on the chemical structure of their side-chain moieties: isoquinoline, *N*-

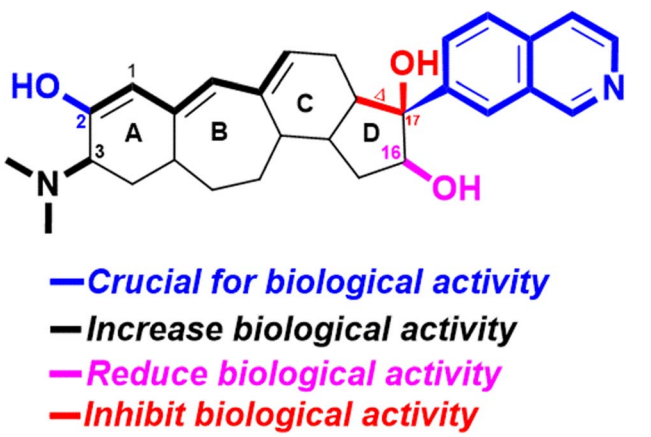


Fig. 4 Key Pharmacophoric SARs linked to cortistatins' s bioactivity.

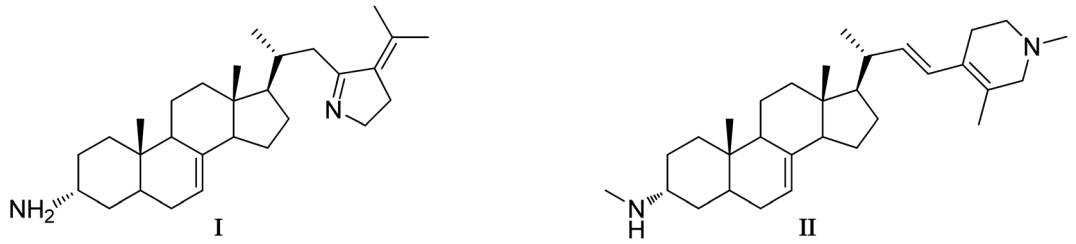


Fig. 5 Chemical structure of plakinamines A–B (I–II).

methyl piperidine, or 3-methylpyridine units.[32,33] Among the recovered cortistatins derivatives, cortistatin A (**3**) and J (**11**), which characterized by a dimethylamino group at the C-3 position and an isoquinoline side chain, were found to be the most active members of this derivatives.[42] The isoquinoline moiety is required for cortistatins and related compounds to display anti-angiogenic activity against HUVECs as evidenced by lack of activity observed with compounds bearing *N*-methyl piperidine (cortistatins E (**7**) and F (**8**)), or 3-methylpyridine unit and/or 22-ene (cortistatin G (**9**) and F (**10**)), showed only weak anti-proliferative activity lost selectivity function.[32] Indeed, the triene system in cortistatin J (**11**) not only exhibited high cytostatic anti-proliferative activity at a concentration of 8 nM but also demonstrated remarkable selectivity against HUVECs compared to other cell lines. This can be further substantiated by the observed decrease in activity and selectivity of cortistatins K (**12**) and L (**13**), which contain a diene system instead of a triene one (Fig. 4).

Additionally, in a study by Naoyuki *et al.*, the position of the side chain was shown to be critical, as the target molecule strictly recognizes cortistatins with an isoquinolin-7-yl moiety. Synthetic analogues containing an isoquinolin-6-yl moiety were able to interact with the target molecule but resulted in a significant loss of activity, with less than half the maximal inhibitory concentration.[43]

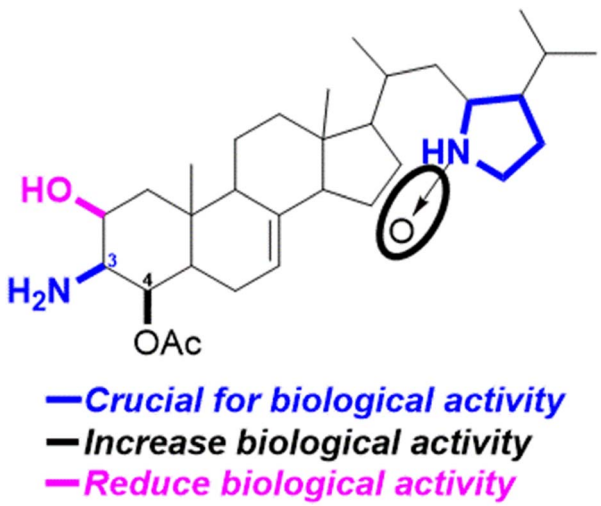


Fig. 6 Key pharmacophoric SARs linked to plakinamines' s bioactivity.

Additionally, 2a-hydroxyl-diene nature of cortistatins L (**13**) and the absence of hydroxylation at the 2-position in cortistatin K (**12**) further exacerbates the decline in bioactivity and selectivity.[44] Accordingly, it can be concluded that conjugation plays a more critical role in selectivity than the presence/absence of the hydroxyl group on ring A.[45] However, this does not extend to ring D, as hydroxylation, particularly at the 16- or 17-positions, as seen in cortistatins B (**4**) and D (**6**), significantly reduces activity.[12]

Furthermore, in a related synthetic study, estrogen analogues lacking the tertiary amine group at the C-3 position retained inhibitory activity but exhibited a threefold reduction in potency. Notably, the C-17 Δ-analogue failed to demonstrate any inhibitory effect on the cell lines tested.[44] Moreover, Phil S. Baran and his co-workers studied the effect of stereochemistry of C-17 on biological activity. The authors showed that 17-*epi*-cortistatin A does not exhibit significant activity, indicating the importance of stereochemistry for biological behaviour.[19] (Fig. 4).

4.2 Plakinamines structure activity relationships

In general, plakinamine A analogues has emerged as the predominant and highly potent cytotoxin within the plakinamines class, the cytotoxic activity of plakinamines A–B (**I–II**) (Fig. 5), G (**23**),[36] J (**28**),[37] K (**29**),[37] N (**35**),[40] O (**36**)[40] with substituted pyrrolidine ring in their steroidal side chains showed the highest activity regardless of the presence of the Δ^{24} olefin as in dihydroplakinamine K (**30**).[37] In contrast, plakinamine I (**27**)[37] featuring a fused piperidine ring showed reduction in cytotoxicity as evidenced by a low cytotoxic activity against the human colon tumour cell line HCT-116.[40]

Furthermore, A cell line-dependent cytotoxicity profile was observed within this class of compounds, for instance, plakinamine G (**23**)[36] and tetrahydroplakinamine A (**26**) exhibited higher activity against rat glioma (C6) cells, whereas plakinamine H (**24**) and hydroxydemethylplakinamine B (**25**) demonstrated greater selectivity towards murine monocyte/macrophage (RAW 264) cell lines. Overall, these results revealed that plakinamines with a saturated pyrrolidine ring in their side chain exhibited greater cytotoxic activity compared to those containing a tetrahydropyridine ring, additionally when the acetate group was placed at C-4 as observed in plakinamine K (**29**) and plakinamine O (**36**), an increase in cytotoxic activity was observed.[36] (Fig. 6).

Moreover, De Marino *et al.*, have investigated the cytotoxic activity of plakinamine C (**16**) and D (**17**),[16] characterized by the ketone carbon atom C-4 of the steroid nucleus and an ethanolamine residue bonded to the pyrrolidine ring through the nitrogen atom. Plakinamine D (**17**) showed superior cytotoxic activity to *N*,*N*-dimethyl-4-oxo-3-*epi*-plakinamine B (**18**) and 24,25-dihydroplakinamine A (**19**) when tested against NSCLC-N6 Cells with IC_{50} < 3.3 μg mL^{-1}.[16] Indeed, the replacement of the imine group in the side chain of lokysterolamine A (**14**) with a nitrone group significantly enhanced the cytotoxic activity against the human leukaemia cell line K562, as observed with plakinamine E (**21**).[35]

Conversely, the oxidation of the hydroxyl-bearing C-4 position to a carbonyl group, as in plakinamine F (**22**), resulted in a six-fold reduction in cytotoxic activity.[37] Indeed, the majority of plakinamine compounds feature an intact cyclic amine functionality on their side chains, which is critical for their activity. Even though, the substituted pyrrolidine ring demonstrated higher cytotoxicity, plakinamines B (**II**) and H (**24**) featuring an *N*-methyl 1,2,5,6-tetrahydropyridine side chain, exhibited significantly higher antimicrobial activity. A study conducted by Markus *et al.*[46] on the total synthesis of plakinamine B (**II**), synthetic analogues with similar structures, where the methylamino group was replaced by a 3-acetoxy group, showed a marked reduction in activity[46] highlighting the crucial role of the amino group at C-3 in maintaining biological activity, irrespective of its methylation state.[46] Moreover, plakinamines L (**33**),[41] M (**34**),[39] and N (**35**),[47] featuring acyclic side chains, exhibited weak activity against *Candida albicans*. Furthermore, the inhibition of Mtb by plakinamines L (**33**), M (**34**), and N (**35**) revealed significant differences in potency, with MIC values of 3.6 μg mL^{-1}, 15.8 μg mL^{-1}, and 1.8 μg mL^{-1}, respectively. The reduced activity of plakinamine M (**34**)[39] is attributed to the presence of a hydroxyl group at C-2, which appears to negatively impact its inhibitory activity. In contrast, the dimethyl amino group in plakinamine M (**34**) enhances its activity with a selectivity index (SI) of 8.5 (ref. 47) (Fig. 6).

5. Pharmacokinetics and drug-likeness properties of cortistatins and plakinamines

A total of 36 cortistatins and plakinamines were characterized from three marine-derived chordates, specifically *Corticium* sp., *C. simplex*, and *C. niger*. These identified compounds exhibit a wide range of potent biological and pharmacological activities, including significant cytotoxic effects against various cancer cell lines, along with antibacterial and antiviral properties. Their diverse potential makes them highly promising candidates for drug discovery. This study highlights the drug-likeness and pharmacokinetic properties of cortistatins and plakinamines, acknowledging the well-documented challenges associated with the pharmacokinetics of natural products. We explore various molecular descriptors to establish rules specific to this category of natural compounds. The calculated properties presented in Table 2 can serve as a valuable reference for future drug discovery projects.

Table 2 Explore based data analysis of eight physicochemical properties of the cortistatins and plakinamines are based on their source producing species[a]

	Source	Mean	Min	Max	Median	Skewness
MW	*Corticium* sp.	467.178	420.685	510.807	466.754	−0.121
	C. simplex	469.572	438.615	502.611	472.629	−0.115
	C. niger	465.424	424.717	498.796	466.754	−0.156
c log *P*	*Corticium* sp.	6.595	5.707	8.055	6.539	1.025
	C. simplex	5.306	2.631	6.744	6.182	−0.698
	C. niger	6.524	6.158	6.924	6.518	0.201
nHD	*Corticium* sp.	1.052	0.000	2.000	1.000	−0.025
	C. simplex	1.000	0.000	3.000	0.000	0.724
	C. niger	1.500	0.000	2.000	2.000	−1.536
nHA	*Corticium* sp.	2.842	2.000	4.000	3.000	0.286
	C. simplex	4.181	3.000	7.000	3.000	0.842
	C. niger	3.000	2.000	4.000	3.000	0.000
TPSA	*Corticium* sp.	38.976	6.480	61.690	38.380	−0.537
	C. simplex	46.939	15.710	103.120	25.360	0.715
	C. niger	39.810	6.480	64.350	44.205	−0.761
RB	*Corticium* sp.	4.684	3.000	8.000	4.000	1.344
	C. simplex	3.000	2.000	5.000	2.000	0.777
	C. niger	3.833	1.000	6.000	4.000	−0.678
NC	*Corticium* sp.	4.894	4.000	5.000	5.000	−2.798
	C. simplex	6.636	6.000	7.000	7.000	−0.660
	C. niger	5.166	5.000	6.000	5.000	2.449
Log *S*	*Corticium* sp.	−5.249	−6.514	−4.292	−5.119	−0.340
	C. simplex	−4.208	−5.523	−2.724	−4.383	−0.221
	C. niger	−4.662	−4.873	−4.298	−4.721	−0.635

[a] In addition to the eight physicochemical drug-like properties previously discussed, two additional parameters, namely, quantitative estimate of drug-likeness (QED)[51] and synthetic accessibility (SA)[52] scores have been utilized to evaluate the ligandability of the 36 compounds.

5.1 Drug likeness of cortistatins and plakinamines

Oral bioavailability describes how effectively a drug can be absorbed when taken orally. This concept is closely related to the processes of absorption, distribution, metabolism, excretion, and toxicity (ADME/T) of drug molecules. In simple terms, it describes the ability of a drug to cross through the intestinal walls, enter the bloodstream, reach its target site, and remain there long enough to carry out its intended medical effect. Once it has been eliminated from the body efficiently, it must not accumulate to high levels that can be toxic.

The Rule of Five (Ro5)[48] is a set of four physical-chemical property ranges that can increase the likelihood of a biologically active compound being orally bioavailable and having a favorable ADMET profile. These rules include a molecular weight of less than 500, a *c* log *P* of less than 5, less than 5 hydrogen bond donors (nHD), and less than 10 hydrogen bond acceptors (nHA).

In addition to Lipinski's properties, other parameters have been investigated like Topological Polar Surface Area (TPSA), which is another parameter that can be included in evaluating the oral bioavailability of compounds because TPSA has a substantial effect on the potential of a compound to penetrate

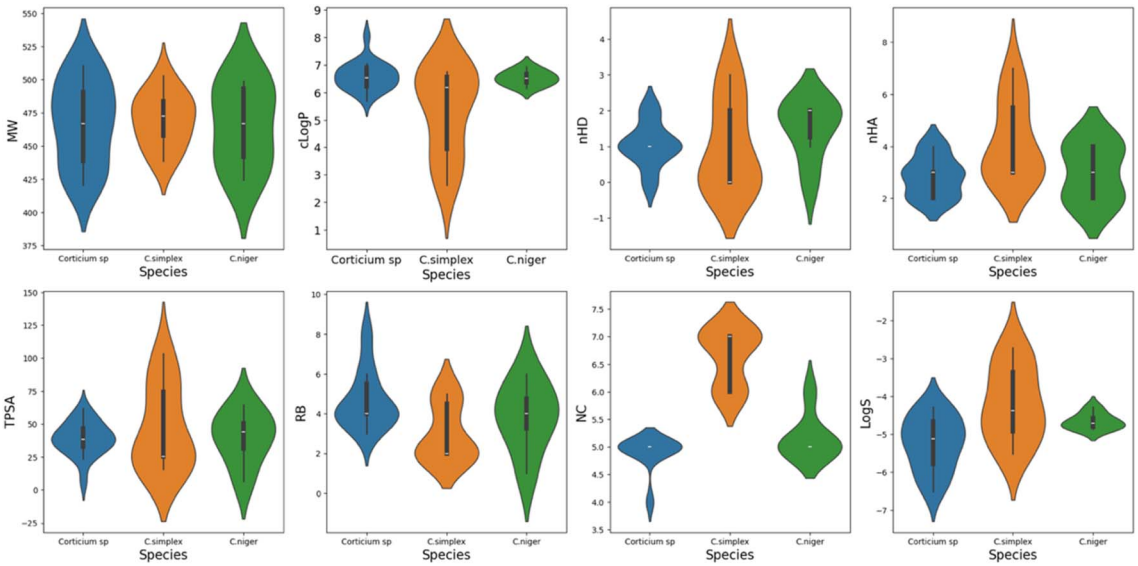


Fig. 7 Distribution of molecular weight (MW), number of hydrogen bond acceptors (nHA), number of hydrogen bond donors (nHD), number of rotatable bonds (RB), topological polar surface area (TPSA), lipophilicity (log *P*), number of ring count (NC) and solubility (log *S*) according to the compound's family producing species *Corticium* sp., *C. simplex* and *C. niger*.

through the cell membranes and blood–brain barrier. Small compounds with TPSA < 140 Å^2 have more chance to be well absorbed and able to reach their molecular target within the body cells, according to Veber,[49] water solubility, which is expressed as log *S*, is another important measure for drug bioavailability.

Indeed, compounds with poor water solubility have poor absorption and oral bioavailability, as well as low formulation potential in drug discovery projects. Water solubility is given in log(mol L^{-1}) (insoluble ≤ -10 < poorly soluble ≤ -6 < moderately ≤ -4 < soluble ≤ -2 < very soluble < 0 < highly soluble).[50] All the eight investigated physicochemical properties exhibit nonparametric distribution patterns, as shown in Fig. 7 and Table 2. The compounds studied from the three species exhibit generally acceptable drug-like physicochemical properties, except for *c* log *P*. Compounds produced by *Corticium* sp. and *C. niger* show higher lipophilicity compared to those from *C. simplex*, as depicted in Fig. 7.

Additionally, all molecules display a certain degree of flexibility and possess *c* log *P* values that exceed the typical parameters defined by drug-like criteria, contributing to their lipophilic nature. Three compounds, specifically **3**, **4**, and **5**, exhibit all drug-like properties without violations and, therefore, have a *c* log *P* of less than **5**. About other molecular drug-like filters, Table S2 (ESI†) shows that all compounds respect the Rule of Veber with at least one exception, except for compounds **33** and **34**. Additionally, only compounds **16**, **17**, **31**, and **32** do not comply with the Rule of 3.

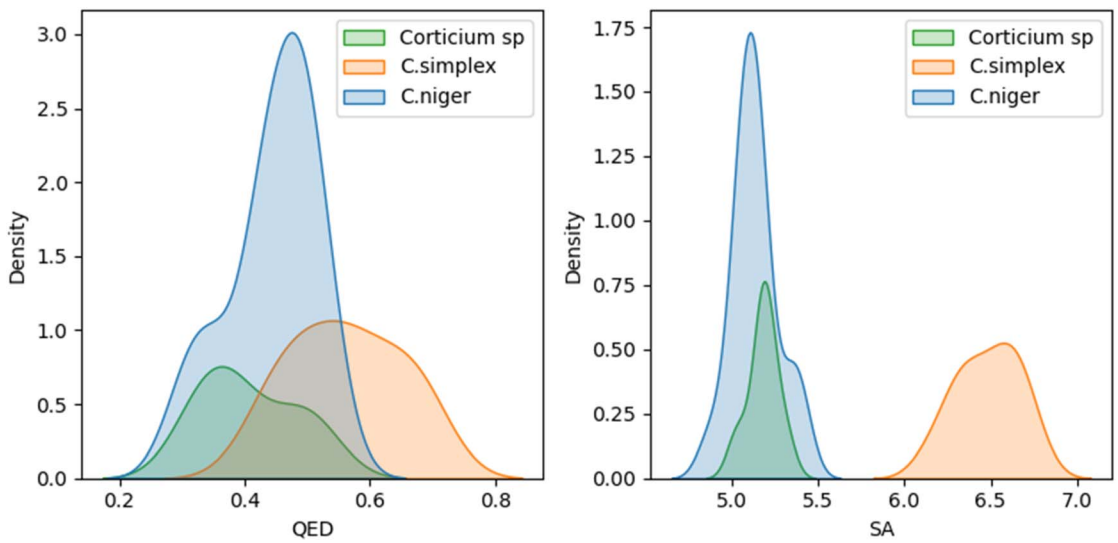


Fig. 8 Distribution of quantitative estimate of drug-likeness (QED) and synthetic accessibility (SA) based on the species of compounds producing cortistatins and plakinamines.

However, all compounds conform to the Rule of 4. If we inspect the properties of these molecules, we can understand that among the compounds with violations, only compounds **33** and **34** are highly lipophilic, with *c* log *P* values of 8.0559 and 7.0267, respectively, and a high degree of flexibility. The solubility profiles of cortistatins and plakinamines indicate that this class of molecules displays a moderate level of solubility. Specifically, the median solubility values calculated for various compounds are as follows: those produced by *C.* sp. had a median solubility of −5.119, which reflects a relatively lower solubility.

In contrast, the compounds derived from *C. simplex* exhibited a median solubility of −4.383, while those from *C. niger* presented a median solubility of −4.721. These findings highlight the differences in solubility across the different species, underscoring the distinct chemical properties associated with each species source. As known the number of orally bioavailable drugs and drug candidates exhibiting one or more Rule of Five (Ro5) violations (bRo5) is steadily on the rise. Currently, compounds with established promising biological activities as anticancer agents are paving the way for new natural product-derived drug candidates that extend beyond the conventional guidelines.

The QED (Fig. 8) serves as an indication of the distribution of Lipinski's molecular properties, with values ranging from zero (indicating all properties are unfavourable) to one (indicating all properties are favourable). Meanwhile, the SA score assesses the ease of synthesizing the compounds, where a score of 0 signifies easy synthesis and a score of 10 indicates significant difficulties in synthesis. According to Fig. 8, the QED median values for cortistatins and plakinamines are approximately 0.46 and 0.60, and 0.38 for *Corticium* sp., *C. simplex*, and *C. niger,* respectively.

Notably, the QED values for compounds produced by *Corticium* sp. and *C. niger* exhibit a skew compared to those from *C. simplex*. In terms of SA median values, they stand at approximately 5.181, 6.493, and 5.106 for *Corticium* sp., *C. simplex*, and *C. niger*, respectively.

This indicates that compounds from *C. simplex* possess higher drug-like properties compared to those derived from the other two species. However, they are challenging to produce, which underscores an important point: while natural products can exhibit promising drug-like characteristics, their laboratory synthesis can be complicated.

Conversely, the compounds from *Corticium* sp. and *C. niger* tend to have lower QED values but are easier to synthesize (SA values between 5.028 and 5.927 Table S1, ESI†).

Based on the discussions above regarding the various properties, it can be concluded that the 36 compounds in question exhibit greater hydrophobicity compared to traditional drug compounds. This observation prompts us to consider additional rules, such as the Rule of 4 (Ro4), applicable to Protein–Protein Interaction Drugs (PPIDs) and Proteolysis Targeting Chimeras (PROTACs).

Notably, all compounds adhere to the Ro4 criteria, as illustrated in Fig. 5 and Table S1 and S2 (ESI†). Each compound demonstrates a molecular weight (MW) greater than 400, a *c* log *P* value exceeding 4, a number of rings (NC) above 4, and more than 4 hydrogen bond acceptors (nHA). Furthermore, these compounds exhibit lower QED values compared to non-PPI drugs, as shown in (Fig. 8), a trend also noted in PPIDs and PROTACs. Consequently, the analysis reveals that alongside the complex and distinctive structures of these 36 compounds compared to traditional small-molecule drugs, cortistatins, and plakinamines possess intriguing characteristics that position them as promising candidates for development as PPIDs and offer potential in the creation of PROTACs,[53] by introducing linkers and E3 ligase inhibitors to those compounds.

5.2 Pharmacokinetics of marine steroidal alkaloids cortistatins and plakinamines

Table S3 (ESI†) summarizes the predicted absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the investigated compounds. We focused on key parameters impacting oral bioavailability. The pkCSM[50] model predicts human oral bioavailability, which reflects the percentage of an orally administered drug that reaches systemic circulation. An intestinal absorbance value below 30% suggests poor absorption.

Here, all compounds are predicted to have excellent intestinal and oral absorption, suggesting good permeability. The low total clearance ($\log CL_{tot}$) values for these compounds suggest a potentially extended drug half-life.

Additionally, a log BB value below −1 indicates poor distribution to the brain. Importantly, none of the compounds exhibited hERG inhibition or tested positive in the AMES test, which implies a minimal risk of cardiac side effects or mutations. However, all compounds display low total clearance values, along with some ability to cross the blood–brain barrier. All compounds are predicted to be inhibitors for CYP1A2, however, there are predicted to be substrates CYP3A4, the two main cytochrome P450 subtypes, which should be considered for further drug discovery projects to investigate metabolism and potential drug–drug interactions.

According to the detailed ADMET analysis (Table S3†), all compounds demonstrate favorable ADMET profiles and may be promising candidates for further experimental investigation. This is particularly noteworthy given that the unique characteristics of natural products often diverge from conventional drug-likeness criteria, such as the Rule of Five (Ro5), yet this does not inherently negate their bioactivity.

While developing them into conventional oral drugs may present challenges, they can still serve as valuable starting points for drug discovery projects. It has been reported that, in the past 40 years, approximately half of the new drugs on the market came directly or indirectly from natural products.[54] Their optimization may include alternative administration routes, modifications to enhance drug-likeness, or exploring new strategies such as PPIDs and PROTACs.

6. Conclusions and future perspectives

The current review explored the immense potential of cortistatins and plakinamines from the marine sponges of the genus

Corticium. as promising candidates for marine-derived drug discovery. It delves into their complex chemistry, covering the isolation and structural elucidation of cortistatins, plakinamines and their related compounds. Besides, it explores the diverse pharmacological activities of these unique steroidal alkaloids, including cytotoxic, immunomodulatory, antimicrobial, antiviral, nucleic acid-cleaving and enzyme inhibitory activities.

The structure–activity relationships (SAR) of cortistatins and plakinamines emphasized the importance of specific functional groups in determining their bioactivity. Cortistatins with an isoquinoline side chain, such as cortistatin A and J, exhibited the strongest anti-angiogenic and anticancer effects, while modifications to the triene system and hydroxylation patterns proved to immensely impact potency and selectivity. Similarly, plakinamines with a substituted pyrrolidine ring demonstrated enhanced cytotoxic and antimicrobial activities, with key structural features like the C-3 amino group and C-4 acetate influencing their bioactivity.

Investigating the drug-likeness and pharmacokinetic properties of the identified 36 cortistatins and plakinamines revealed adherence to various drug-likeness criteria, such as the Rule of Four (Ro4), and demonstrated promise for applications in Protein–Protein Interaction Drugs (PPIDs) and Proteolysis Targeting Chimeras (PROTACs). Notably, while compounds isolated from the marine sponge *Corticium simplex* showed superior drug-like properties but were more challenging to synthesize. Meanwhile, compounds recorded from the other species including *Corticium* sp. and *C. niger* were easier to synthesize but exhibited lower Quantitative Estimate of Drug-likeness (QED) values. Solubility and lipophilicity analyses revealed interspecies variability, with some compounds surpassing typical lipophilicity thresholds. Despite minor violations of Lipinski's Rule of Five, many compounds demonstrated significant drug discovery potential, particularly as anticancer agents, by leveraging both drug-like properties and innovative synthesis strategies.

Furthermore, favorable ADMET profiles, including excellent absorption, extended half-life, and minimal risks of toxicity, reinforced their promise for drug development. These findings highlight the significant therapeutic potential of the marine-derived natural products, cortistatins and plakinamines. These compounds provide a robust foundation for further research into their analogs and related bioactive molecules.

Future directions include the development of optimized synthetic strategies to improve their bioavailability and target specificity, as well as comprehensive exploration of their mechanisms of action and therapeutic applications. Advancing this research will require preclinical and clinical studies, complemented by innovative tools such as computational modeling and structure-based drug design, to fully realize their potential as transformative agents in drug discovery.

Data availability

This is a review article, and no new data were generated or analyzed in this study. All data discussed are based on published literature cited within the manuscript.

Author contributions

Mohamed A. Tammam: writing-original draft, writing-review & editing, visualization, validation, conceptualization, formal analysis, data curation. Adnane Aouidate: writing-review & editing, writing-original draft, formal analysis, data curation. Manar M. Mahmoud: writing-review & editing, writing-original draft, formal analysis, data curation. Mariam I. Gamal El-Din: writing-review & editing, writing-original draft. Amr El-Demerdash: writing-review & editing, writing-original draft, visualization, validation, supervision, project administration, investigation, conceptualization. Formal analysis, data curation.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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