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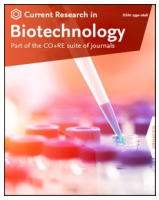

Pederins, mycalamides, onnamides and theopederins: Distinctive polyketide families with intriguing therapeutic potentialities

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ABSTRACT

In this comprehensive review article, an in-depth exploration over the period from 1949 to 2023 is presented, focusing on the discovery, chemistry, biosynthesis and therapeutic potentials of pederin and related polyketides. Herein, we extensively documented a diverse collection of 45 isolated compounds with varied chemical structures, systematically organized based on their isolation sources. Furthermore, it includes an updated detailed overview of their reported pharmacological activities whenever applicable. Additionally, the article briefly discusses insights into the proposed biosynthetic pathway of these intriguing polyketides.

Introduction

Natural products (**NPs**) have long played a vital role in drug discovery and development. They offer a rich source of diverse chemical structures with unique and often complex biological activities. **NPs** provide a clue starting point for drug discovery due to their inherent bioactivityMany important drugs on the market today, as well as those in clinical development, are derived from natural products or inspired by their structures (Huang and Zhang, 2022; Singh et al., 2023). They have evolved in plants, microorganisms, and marine organisms as defence mechanisms or for signalling purposes, making them a valuable resource for identifying potential therapeutic agents. Researchers screen extracts or purified compounds from natural sources against specific disease targets for biological assays to identify promising lead compounds (Atanasov et al., 2021; Cragg et al., 1997; Harvey, 2008). In addition to direct therapeutic agents, **NPs** also serve as scaffolds for synthetic modifications and lead optimization. By manipulating the structures of natural compounds, researchers can enhance their pharmacological properties, such as potency, selectivity, and bioavailability (Buskes et al., 2023; Kumar, 2023).

Recent advancements in isolation, characterization, and synthetic methods have facilitated the discovery and development of natural products. Techniques such as high-throughput screening, combinatorial chemistry, and genomics have enabled researchers to accelerate the identification and evaluation of natural product-based drug candidates (Dias et al., 2012; Harvey et al., 2015; Thomford et al., 2018). Moreover, **NPs** have expanded beyond traditional terrestrial sources, with marine organisms providing a promising avenue for drug discovery. The unique environments and biodiversity of the oceans offer a vast array of natural products with diverse chemical structures and biological activities (Koparde et al., 2019; Lyu et al., 2021; Montuori et al., 2023; Shinde et al., 2019).

Considering that the marine environment is covering nearly 70 % of the entire Earth's surface, it is home to the largest ecological system, hosting an astonishing 92 % of all known phyla. This vast expanse remains largely unexplored, holding immense potential for the discovery of valuable resources. Since the ground-breaking discovery of marine bioactive nucleotides in the 1950s by Brigman *et al.*, marine natural products (**MNPs**) have emerged as a sustainable and prolific source of diverse bioactive compounds. With the identification of over 40,000 compounds, characterized by unique structural features and remarkable biological activities, marine natural products (**MNPs**) have become a central focus in the global drug lead discovery program. The ongoing discovery of hundreds of new MNP chemical entities each year further

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highlights their importance as a source of new drug leads (El-Demerdash, 2018; El-Demerdash et al., 2018a; El-Demerdash et al., 2019; El-Demerdash et al., 2018b). Up to 2023, these fruitful explorations have yielded 17 approved and commercially available marine-based drug leads, with an additional 40 candidates currently undergoing various preclinical investigations. The continuous efforts in this field have not only contributed to expanding our understanding of the marine realm but have also demonstrated the remarkable therapeutic potential of **MNPs** (Almaliti and Gerwick, 2023; Carroll et al., 2023; Ghareeb et al., 2020; Mayer et al., 2010; Montaser and Luesch, 2011; Yeung et al., 2018).

Pederins, mycalamides, onnamides, and theopederins represent distinct families of polyketide-containing nitrogen compounds. These compounds are biosynthetically derived from a gene cluster that combines polyketide synthase (**PKS**) and nonribosomal peptide synthetase (**NRPS**). Structurally, they consist of a core composed of two interconnected tetrahydropyran rings. This core is connected through an *N*-acyl aminal moiety, and adorned with varying degrees of oxidation (Mosey and Floreancig, 2012).

As a part of our continuing research focused on biologically active marine natural products, herein we present a comprehensive literature review spanning the years 1949 to 2023, with emphasis on providing of an up-to-dated overview of the chemical diversity and biological activities associated with pederin-related polyketides (see Table 1).

The review thoroughly documents the distribution of 36 pederin-derived polyketide, emphasizing their varied chemical structures and possible therapeutic applications. It also provides insights into the structure activity relationships (**SAR**) of these compounds. Additionally, we briefly discuss insights into their proposed biogenesis.

Chemistry of pederins, mycalamides, onnamides and theopederins

In this section, all the isolated compounds were listed and systematically classified into four main subcategories according to their molecular architectures.

Pederin polyketides

Pederin (**1**) was initially the first member of these fascinating natural products. It was reported in 1949 from the female beetle *Paederus littoralis*. However, its structure underwent further investigations and was subsequently revised in 1968 to its complete form (Matsumoto et al., 1968). Further efforts by Cardani *et al.*, (Cardani et al., 1965) led to the isolation of pesudopederin (**2**) and pederone (**3**). Furthermore, Schleissner *et al.*, reported for the isolation of further pederin congener namely, 18-*O*-demethylpederin (**4**), for the first time from the free living marine derived bacteria *Labrenzia* sp.PHM005, isolated from a marine sediment collected from the coast of Kenya on 18 m depth (Schleissner et al., 2017). HPLC-MS analysis of the methanol extract of *Diaphorina citri* detects the presence of an additional pederin-related congener, namely diaphorin (**5**) (Ramsey et al., 2015).

Additional members of pederin-polyketides, named Irciniastatin A (**6**) and irciniastatin B (**7**) were isolated from the organic extract of the Indo-pacific marine sponge *Ircinia ramosa* (Pettit et al., 2004). Further pederin-congener, namely psymberin (**8**), a pederin related derivative was isolated from the marine sponge *Psammocinia* sp. (Cichewicz et al., 2004).

Recently, labrenzin (**9**) and its 17-*O*-demethylated analogue (**10**) along with pederin (**1**) were obtained from the marine derived bacterium *Labrenzia* sp. PHM005 (Kačar et al., 2022). Additionally, an examination of the polar extract of the nonsymbiotic cyanobacterium, *Cuspidothrix issatschenkoi* (Usacev) led to the isolation of the novel pederin analogues cusperin A (**11**) and cusperin B (**12**) (Kust et al., 2018) (Chart I).

Mycalamide polyketides

In 1989–1990, Perry *et al.*, documented the discovery of additional structurally related compounds from marine sources. These compounds, named mycalamides A-B (**13**–**14**), were isolated from a marine sponge belonging to the genus *Mycale*, which was collected in New Zealand (Perry et al., 1988; Perry et al., 1990).

Additionally, further two additional compounds, mycalamides C-D (**15**–**16**), where these compounds were isolated from marine sponges belonging to the genera *Stylinos* and *Mycale* (Simpson et al., 2000; West et al., 2000). In a separate study, Venturi *et al.,* identified the last member of this family, mycalamide E (**17**), from the marine sponge *Mycale hentscheli* found in Pelorus Sound, New Zealand (Venturi et al., 2012). Additionally, Zimmermann *et al.,* reported the synthesis of 18-*O*-Methylmycalamide A (**18**), from its natural analogue mycalamide A (**13**) (Zimmermann et al., 2009) (Chart II**).**

Onnamide polyketides

Onnamides (**19**–**33**) represent the largest subgroup within this compound family. They feature an arginyl amino acid residue, linked to unsaturated fatty acid chain through an amidic linkage. They have been isolated from marine sponges of the genera *Theonella* and *Trachycladus* (Kobayashi et al., 1993; Matsunaga et al., 1992; Nakamura et al., 2023; Sakemi et al., 1988; Vuong et al., 2001) **(**Chart II and Chart IV**).**

Theopederin polyketides

Theopederins A-J (**34**–**43**) were originally reported from marine sponges of the genus *Theonella* (Fusetani et al., 1992; Tsukamoto et al., 1999), whereas theopederins K-L (**44**–**45**) were identified from a marine sponge known as *Discodermia* sp., (Paul et al., 2002) (Chart V).

Detailed therapeutic potentialities

Pharmacologically, pederin-containing compounds are best categorized as protein synthesis inhibitors. This classification endows them with a diverse range of biological activities. In this section, their detailed biological activities are classified and discussed accordingly wherever applicable.

Cytotoxic and anti-tumour activities

In 1966, Soldati, Fioretti, and Ghione were the first to report the cytotoxicity of pederin (**1**) and its related derivatives. They proceeded to conduct screenings of these compounds against various normal and cancerous cell lines in order to gain a better understanding of the observed biological properties of these natural toxins. Normal and HeLa cells were exposed to pederin and its related compounds, namely pseudopederin, dihydropederin, and dihydropseudopederin, and the resulting cellular changes were observed 24 h after treatment. At a concentration of 2 nM, all compounds except pseudopederin induced significant cytological alterations, including inhibition of mitosis, fragmentation of nuclear chromatin, cellular bursting, and vacuolization.

Furthermore, complete cell lysis was observed when pederin and dihydropederin were administered at concentrations of 20 nM. (Brega et al., 1968; Hood et al., 2001; Ogawara et al., 1991; Soldati et al., 1966). Even though pederin (**1**), is known to be the best cytotoxin agent belonging to the tetrahydropyran polyketides, its derivative 18-*O*-demethylpederin (**4**), displayed no cytotoxic effect when examined against A549, HT-29, MDA-MB-231 and PSN-1 cancer cell lines (Schleissner et al., 2017). Irciniastatins A (**6**) and B (**7**), displayed strong cytotoxic effect against BXPC-3 (pancreas), MCF-7 (breast), SF268 (CNS), NCI-H460 (lung), KM20L2 (colon), DU-145 (prostate) and P388 (leukemia) human cancer cell lines with GI_{50} values ranged from $<$ 0.0001 to 0.006 μg/mL (Nakabachi and Okamura, 2019). Additionally,

Table 1
List of 45 isolated pederin-containing polyketids along with their isolation and displayed therapeutic activities.

No.	MF Name	Bioactivity	Source	Reference
1	$C_{25}H_{45}NO_9$ Pederin	Cytotoxic, Insecticidal and antifungal effect	*Paederus littoralis*, *Labrenzia* sp. PHM005, *Citrus psyllid*	(Matsumoto et al., 1968; Ogawara et al., 1991; Hood et al., 2001; Brega et al., 1968; Soldati et al., 1966), Kačar et al., 2022
2	$C_{24}H_{43}NO_9$ Pesudopederin	Not determined for any relevant biological activity	*Paederus iuaoipea* Curt	(Cardani et al., 1965)
3	$C_{25}H_{43}NO_9$ Pederone	Not determined for any relevant biological activity	*Paederus littoralis*	(Matsumoto et al., 1968)
4	$C_{24}H_{43}NO_9$ 18-*O*-demethylpederin	Displayed no cytotoxicity	marine derived bacteria *Labrenzia* sp. PHM005	(Schleissner et al., 2017)
5	$C_{22}H_{39}NO_9$ Diaphorin	Insecticidal and antifungal effect	*Diaphorina citri, Citrus psyllid*	Ramsey et al., 2015
6	$C_{31}H_{47}NO_{11}$ Irciniastatin A	Cytotoxic	*Ircinia ramosa*	Pettit et al., 2004
7	$C_{31}H_{45}NO_{11}$ Irciniastatin B	Cytotoxic	*Ircinia ramosa*	Pettit et al., 2004
8	$C_{31}H_{47}NO_{11}$ Psymberin	Cytotoxic	*Psammocinia* sp	Cichewicz et al., 2004
9	$C_{24}H_{43}NO_9$ Labrenzin	Not determined for any relevant biological activity	*Labrenzia* sp. PHM005	Kačar et al., 2022
10	$C_{23}H_{41}NO_9$ 17-*O*-demethylated labrenzin	Not determined for any relevant biological activity	*Labrenzia* sp. PHM005	Kačar et al., 2022
11	$C_{26}H_{42}N_4O_8$ Cusperin A	Not determined for any relevant biological activity	The nonsymbiotic cyanobacterium, *Cuspidothrix issatschenkoi* (Usacev)	Kust et al., 2018
12	$C_{25}H_{40}N_4O_8$ Cusperin B	Not determined for any relevant biological activity	The nonsymbiotic cyanobacterium, *Cuspidothrix issatschenkoi* (Usacev)	Kust et al., 2018
13	$C_{24}H_{41}NO_{10}$ Mycalamide A	Cytotoxic, Antiviral	*Mycale* sp, *Mycale hentscheli*	(Perry et al., 1988; Perry et al., 1990; Venturi et al., 2012; Burres and Clement, 1989)
14	$C_{25}H_{43}NO_{10}$ Mycalamide B	Cytotoxic, Antiviral	*Mycale* sp	(Perry et al., 1990; Burres and Clement, 1989; Piel et al., 2004)
15	$C_{23}H_{41}NO_9$ Mycalamide C	Cytotoxic	*Stylinos* n. sp	(Simpson et al., 2000)
16	$C_{23}H_{39}NO_{10}$ Mycalamide D	Cytotoxic	*Stylinos* n. sp	(Simpson et al., 2000)
17	$C_{23}H_{39}NO_{10}$ Mycalamide E	Not determined for any relevant biological activity	*Mycale hentscheli*	(Venturi et al., 2012)
18	$C_{25}H_{43}NO_{10}$ 18-*O*-Methylmycalamide A	Cytotoxic	A synthetic analogue	Zimmermann et al., 2009
19	$C_{40}H_{65}N_5O_{12}$ Onnamide A	Cytotoxic	*Theonella* sp, *Theonella conica*	(Matsunaga et al., 1992; Kobayashi et al., 1993; Nakamura et al., 2023; Burres and Clement, 1989)
20	$C_{38}H_{61}N_5O_{12}$ 13-des-*O*-methylonnamide A	Cytotoxic	*Theonella* sp	(Matsunaga et al., 1992)
21	$C_{39}H_{65}N_5O_{12}$ Dihydroonnamide A	Cytotoxic	*Theonella* sp, *Theonella conica*	(Matsunaga et al., 1992; Kobayashi et al., 1993; Nakamura et al., 2023)
22	$C_{37}H_{61}N_5O_{12}$ Onnamide B	Cytotoxic	*Theonella* sp, *Theonella conica*	(Matsunaga et al., 1992; Nakamura et al., 2023)
23	$C_{37}H_{59}N_5O_{12}$ 17-Oxo-onnamide B	Cytotoxic	*Theonella* sp	(Matsunaga et al., 1992)
24	$C_{39}H_{61}N_5O_{14}$ Onnamide C	Cytotoxic	*Theonella* sp	(Matsunaga et al., 1992)
25	$C_{39}H_{64}N_5O_{11}$ Onnamide D	Cytotoxic	*Theonella* sp	(Matsunaga et al., 1992)
26	$C_{37}H_{61}N_5O_{10}$ Onnamide E	Displayed no cytotoxicity	*Theonella* sp	(Matsunaga et al., 1992)
27	$C_{38}H_{61}N_5O_{12}$ Pseudoonnamide A	Not determined for any relevant biological activity	*Theonella* sp	(Matsunaga et al., 1992)
28	$C_{39}H_{63}N_5O_{12}$ 6,7-dihydro-l1-oxo-onnamide A	Cytotoxic	*Theonella* sp	(Kobayashi et al., 1993)
29	$C_{39}H_{61}N_5O_{12}$ 11-Oxo-onnamide A	Cytotoxic	*Theonella* sp	(Matsumoto et al., 1968; Ogawara et al., 1991; Hood et al., 2001; Brega et al., 1968; Soldati et al., 1966)
30	$C_{31}H_{51}NO_{10}$ Onnamide F	Nematocidal, Antifungal	*Trachycladus laevispirulifer*	(Cardani et al., 1965)
31	$C_{39}H_{63}N_5O_{12}$ 4*Z*-Onnamide A	Cytotoxic	*Theonella* sp, *Theonella conica*	(Matsumoto et al., 1968)
32	$C_{39}H_{63}N_5O_{12}$ 2*Z*-Onnamide A	Cytotoxic	*Theonella conica*	(Schleissner et al., 2017)
33	$C_{39}H_{63}N_5O_{12}$ 6*Z*-Onnamide A	Cytotoxic	*Theonella conica*	(Perry et al., 1988; Perry et al., 1990; Venturi et al., 2012; Burres and Clement, 1989)

(*continued on next page*)

Table 1 (*continued*)

No.	MF Name	Bioactivity	Source	Reference
34	$C_{27}H_{45}NO_{10}$ Theopederin A	Cytotoxic	*Theonella* sp	(Perry et al., 1990; Burres and Clement, 1989; Piel et al., 2004)
35	$C_{28}H_{47}NO_{11}$ Theopederin B	Cytotoxic	*Theonella* sp	(Simpson et al., 2000)
36	$C_{27}H_{43}NO_{10}$ Theopederin C	Cytotoxic	*Theonella* sp	(Simpson et al., 2000)
37	$C_{26}H_{41}NO_{10}$ Theopederin D	Cytotoxic	*Theonella* sp	(Venturi et al., 2012)
38	$C_{22}H_{37}NO_{9}$ Theopederin E	Cytotoxic	*Theonella* sp	(Matsunaga et al., 1992; Kobayashi et al., 1993; Nakamura et al., 2023; Burres and Clement, 1989)
39	$C_{27}H_{47}NO_{10}$ Theopederin F	Cytotoxic, Antifungal	*Theonella* sp	(Matsunaga et al., 1992)
40	$C_{30}H_{47}NO_{11}$ Theopederin G	Cytotoxic, Antifungal	*Theonella* sp	(Matsunaga et al., 1992; Kobayashi et al., 1993; Nakamura et al., 2023)
41	$C_{30}H_{45}NO_{10}$ Theopederin H	Cytotoxic, Antifungal	*Theonella* sp	(Matsunaga et al., 1992; Nakamura et al., 2023)
42	$C_{32}H_{49}NO_{11}$ Theopederin I	Cytotoxic, Antifungal	*Theonella* sp	(Matsunaga et al., 1992)
43	$C_{32}H_{51}NO_{11}$ Theopederin J	Cytotoxic, Antifungal	*Discodermia* sp	(Matsunaga et al., 1992)
44	$C_{32}H_{49}NO_{11}$ Theopederin K	Cytotoxic	*Discodermia* sp	(Matsunaga et al., 1992)
45	$C_{31}H_{47}NO_{11}$ Theopederin L	Cytotoxic	*Discodermia* sp	(Matsunaga et al., 1992)

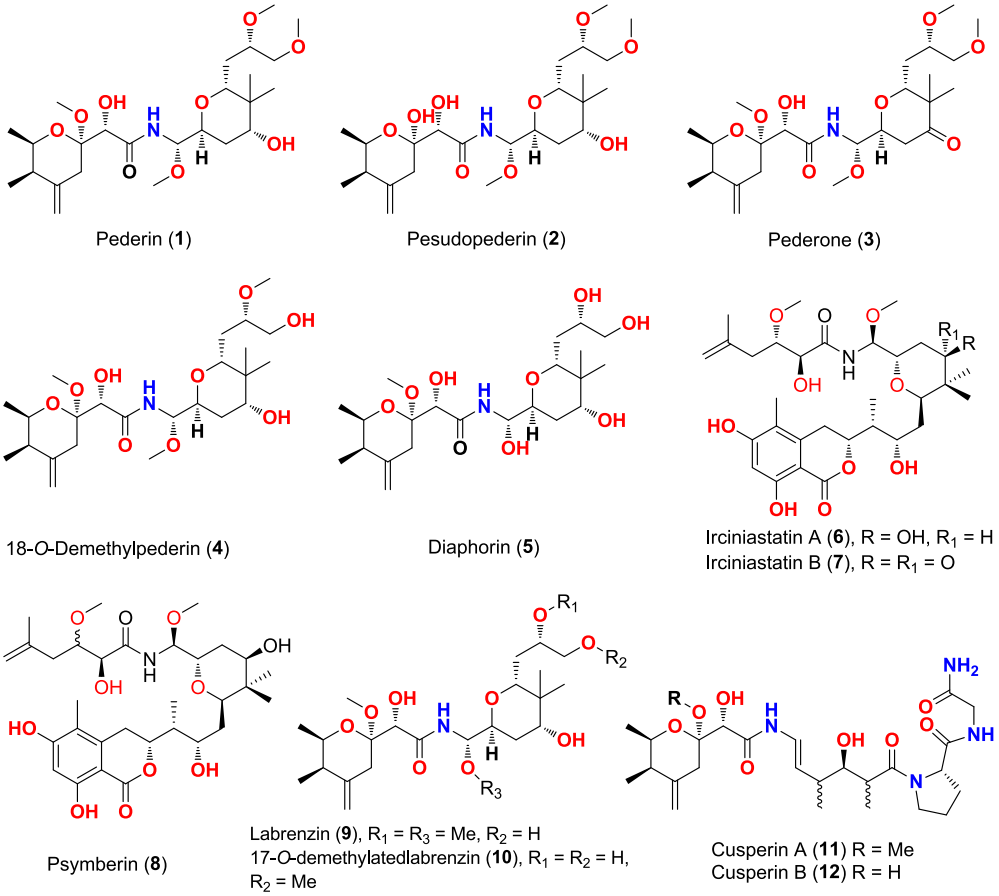

Chart I. Reported pederins **1**–**12.**

irciniastatin A (**6**) was found to be a TNF-α-induced nuclear translocation of NF-κB subunits inhibitor (Hirano et al., 2015). Psymberin (**8**), displayed a potent cytotoxicity against a wide panel of cancer cell lines including leukemia, breast cancer, melanoma and colon cancer cell lines (Cichewicz et al., 2004).

After the structures of mycalamides A and B (**13 and 14**) and onnamide A (**19**) were elucidated, further biological investigations were performed. Burres and Clement were among the first to report on the

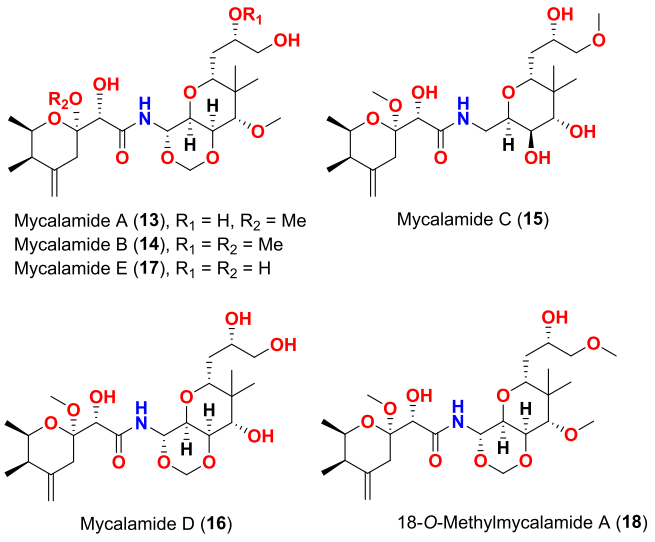

Chart II. Reported mycalamides **13**–**18.**

anti-tumor effects of these pederin-derived natural products. Mycalamides (**13**–**18**, Chart II), are well known to be a potent antitumor agent, mycalamide B (**14**) was a potent cytotoxic agent with IC_{50} value of 0.7 nM, then mycalamide A (**13**) 3.0 nM, when examined against P388 cancer cell line (Perry et al., 1990). Additionally, mycalamides C (**15**) and D (**16**), displayed mild antitumor activity against P-388 murine leukemia cell line with IC_{50} value of 95.0 and 35.0 nM, respectively (Simpson et al., 2000). Furthermore, mycalamide A (**13**) displayed cytotoxicity against HL60, HepG2, A2780 and A2780^{AD} cancer cell lines with IC_{50} values of 4.49, 0.77, 1.06 and 18.90 nM, respectively, it is worth mention that mycalamide E (**17**) was not examined for any relevant biological activity due to lack of quantity (Venturi et al., 2012). Furthermore, 18-*O*-methylmycalamide A (**18**) displayed cytotoxic effect against P-388 cancer cell line with IC_{50} value of 0.07 ng/cm^3 (Zimmermann et al., 2009).

Indeed, these compounds exhibited remarkable effects on the survival of mice with ascitic P388 lymphoma and different types of ascitic and solid tumours. Notably, the administration of mycalamides A and B (**13** and **14**) to mice with interperitoneal (i.p.) 388 leukemia tumors resulted in a significant increase in lifespan. The administration of mycalamide A (**13**) at a dose of 10 μg/kg increased lifespan by 40 %, while mycalamide B (**14**) at a dose of 2.5 μg/kg increased lifespan by 50 %. On the other hand, mycalamide A (**13**) demonstrated at least moderate activity against 9 out of the 11 i.p. and subcutaneous tumor models tested, while mycalamide B (**14**) showed activity against 6 out of 8 models (Burres and Clement, 1989).

In the *in vivo* assay, onnamide A (**19**) exhibited significantly lower potency, with a treatment dose of 40 mg/kg resulting in only a 15 % increase in lifespan. The authors speculated that the reduced *in vivo* potency of onnamide A (**19**) could be attributed to the presence of the charged arginyl group, which may limit its passive diffusion into cells at physiological pH. In contrast, onnamide A (**19**) exhibited activity against only 3 out of 7 models. *In vitro*, these three anti-tumor compounds [(mycalamide A (**13**), mycalamide B (**14**) and onnamide A (**19**)] displayed low nanomolar IC_{50} values (1–5 nM) for inhibiting P388 cell replication. The authors further investigated the mechanism of cytotoxicity of mycalamides A and B (**13** and **14**), as well as onnamide, and concluded that their activity might be attributed to their ability to

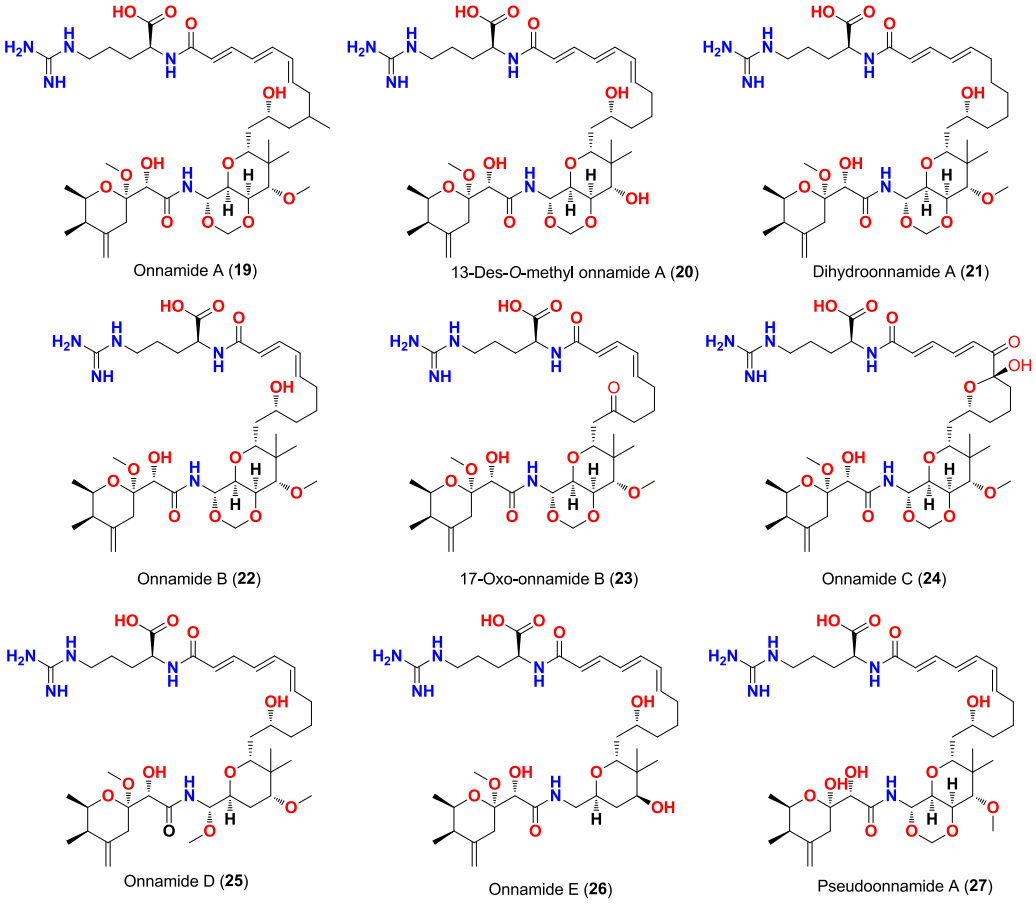

Chart III. Reported onnamides **19**–**27.**

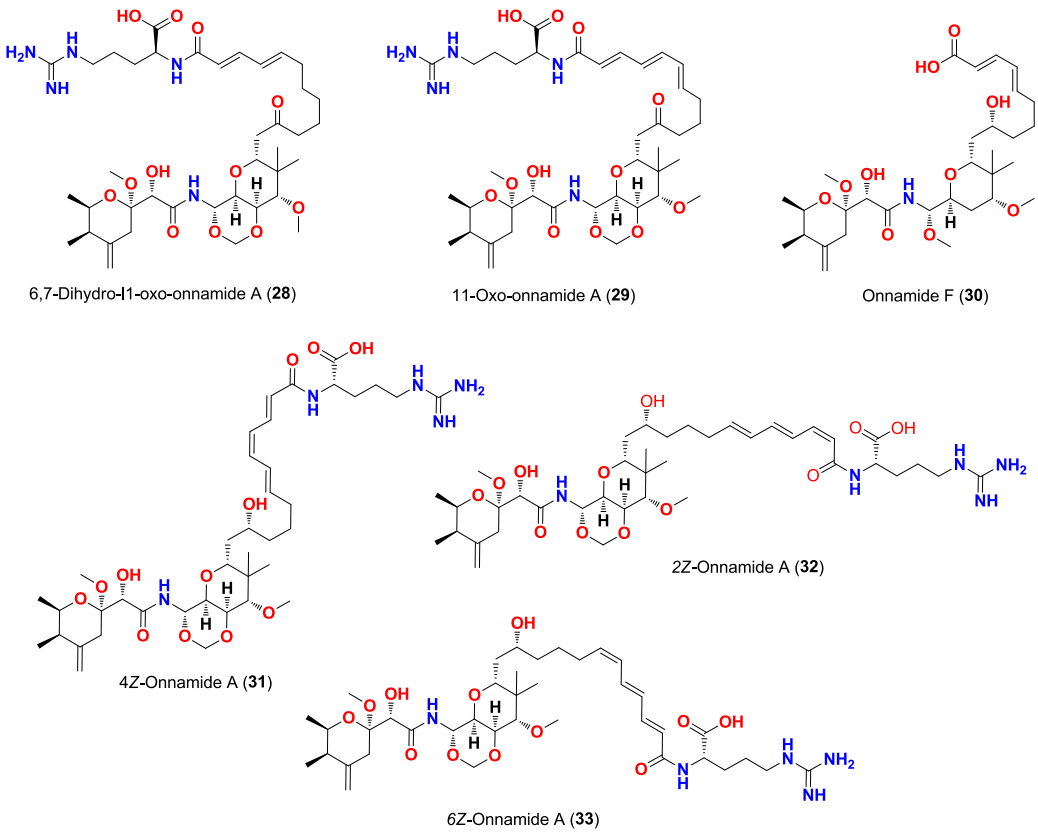

Chart IV. Reported onnamides **28**–**33.**

inhibit protein synthesis (Burres and Clement, 1989).

Additionally, Matsunaga *et al.,* examined the cytotoxic potentialities of onnamide A (**19**), 13-des-*O*-methyl onnamide A (**20**), dihydro onnamide A (**21**), onnamide B (**22**), 17-oxo-onnamide B (**23**), onnamide C (**24**), onnamide D (**25**), and onnamide E (**26**) against P-388 cancer cell line. Compounds **10**–**16** displayed potent cytotoxicity with IC_{50} values of 0.01, 0.15, 0.04, 0.13, 0.10, 0.07 and 0.02 μM, respectively, however onnamide E (**26**) was found to be inactive (Matsunaga et al., 1992).

Subsequently, Kobayashi *et al.,* re-evaluate the cytotoxicity of onnamide A (**19**), dihydro onnamide A (**21**), 6,7-dihydro-l1-oxo-onnamide A (**28**), 11-oxo-onnamide A (**29**), and 4*Z*-onnamide A (**31**) against two human epidermoid carcinoma KB and lymphoma L1210 cancer cell lines, where they displayed a significant antitumor activity with IC_{50} values of (0.0036, 0.005, 0.023, 0.013 and 0.0029) and (0.002, 0.0046, 0.016, 0.0092 and 0.0015) μM, respectively (Kobayashi et al., 1993).

Most recently in 2023, Nakamura *et al.,* evaluate the antitumor effect of the recently identified 2*Z*-onnamide A (**32**) and 6*Z*-onnamide A (**33**) as well as the previously reported onnamide A (**19**), dihydroonnamide A (**21**), onnamide B (**22**) and 4*Z*-onnamide A (**31**), against Hela and P-388 cancer cell lines, and they were found to be potent antitumor agents against the examined cancer cell lines with IC_{50} values ranged from 38 to 540 nM (Nakamura et al., 2023).

Fusetani *et al.,* (Fusetani et al., 1992), mentioned that theopederins A-E (**34**–**38**), displayed a remarkable cytotoxic effect towards P-388 murine leukemia cancer cells with IC_{50} values of 0.05, 0.1, 0.7, 1.0, and 9.0 nM, respectively. Moreover a promising antitumor effect was observed for theopederins A-B (**34**–**35**), aganist P388 (i.p.), with a T/C of −205 and −173 %, respectively. Additionally, while theopederin F (**39**) showed a potent cytotoxic effect towards P388 leukemia cancer cells, with IC_{50} value of 0.15 nM, theopederins G-J (**31**–**34**), exhibited weak cytotoxic activity with IC_{50} values of < 90 nM (Tsukamoto et al., 1999).

Furthermore, the *in vitro* cytotoxic ability of theopederins K (**44**) and L (**45**), against P388 and A549 cancer cell lines were discussed in 2002 by Paul *et al.*, and they were found to display strong to moderate anticancer effect aganist P-388 and A-549 cancer cell lines with IC_{50} values of (0.1/7.3) and (1.5/3.2) nM, respectively (Paul et al., 2002).

Antiviral activity

Perry *et al.*, highlighted that the marine sponge *Mycale* sp., extract displayed *in vitro* potent antiviral activity when tested against a panel of viral targets including coronavirus, herpes simplex virus type-1, vesicular stomatitis virus. Such significant activity attracted their attention to examine the antiviral activity of pure mycalamide A (**13**) against Polio Type I viruses and herpes simplex virus type-1, where mycalamide A (**13**) displayed a strong cytopathic inhibitory activity against both examined viruses with a minimum dose of 5 ng/disk (Perry et al., 1988). Subsequently, Perry *et al.*, studied the antiviral potentiality of mycalamide B (**14**) against Polio Type I viruses and herpes simplex virus type-1, where it was found to be more potent antiviral agent against the tested viruses with a minimum dose of 1–2 ng/disk, than mycalamide A (**13**) (Perry et al., 1990).

Anti-parasitic activity

Pederin (**1**) and diaphorin (**5**) displayed insecticidal effect against *Spodoptera frugiperda*, where diaphorin (**5**) was less toxic than pederin (**1**) (Yamada et al., 2019). Vuong *et al.*, examined the anti-parasitic activity of onnamide F (**30**) to control the parasitic *Haemonchus contortus* nematode growth. Interestingly onnamide F (**30**) displayed strong antinematocidal activity with LD_{99} value of 5.2 μg/mL. Furthermore, onnamide F (**30**) negatively affects larval development at the L1 larval stage within higher concentration (Vuong et al., 2001).

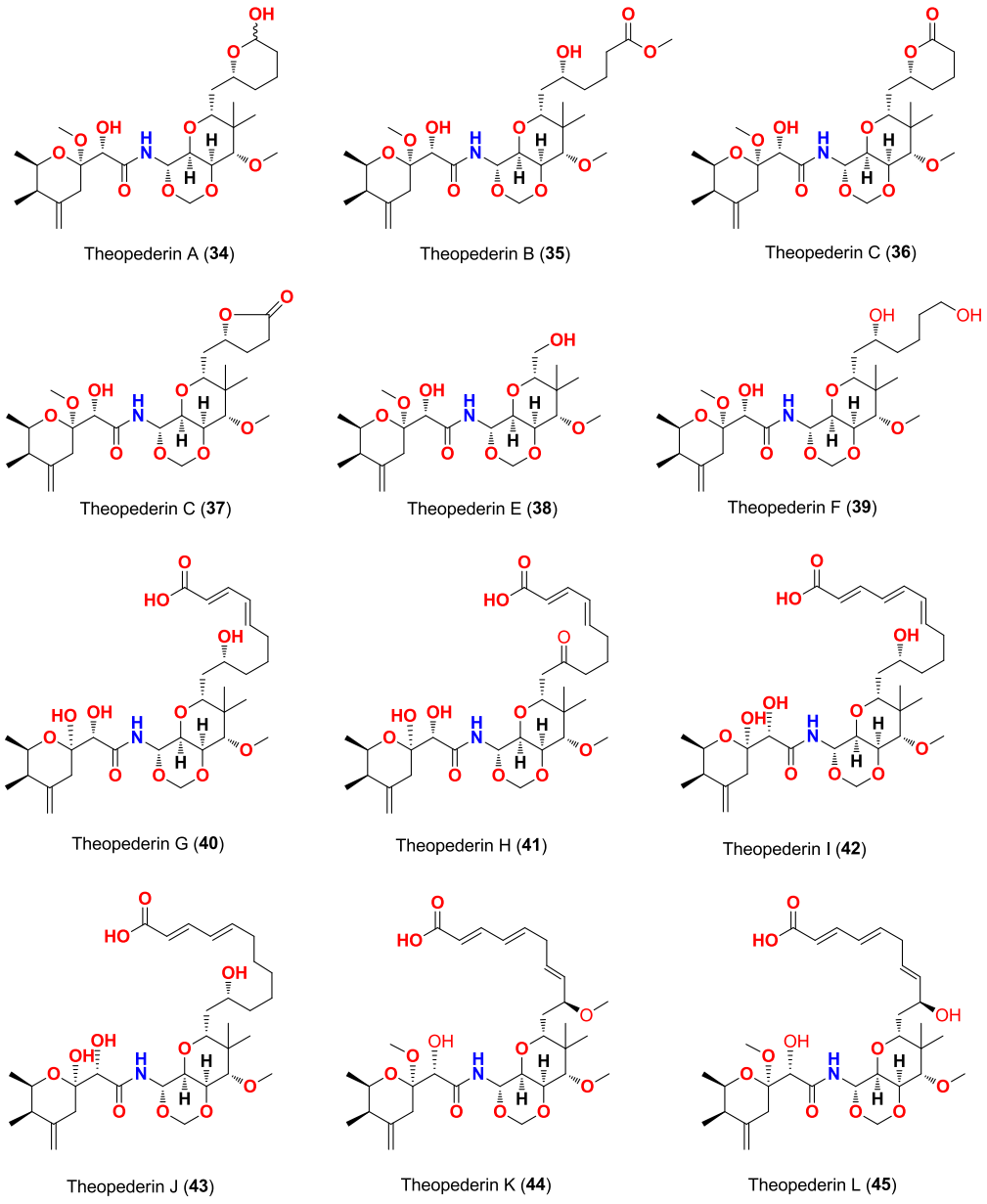

Chart V. Reported theopederins **34**–**45.**

Antifungal activity

Pederin (**1**) and diaphorin (**5**) were found to be antifungal agent against the yeast *Saccharomyces cerevisiae* BY4741, pederin (**1**) was more toxic than diaphorin (**5**) (Yamada et al., 2019). Theopederin F (**39**) displayed antifungal activity against *Saccharomyces cerevisiae* with a growth inhibitory zone of 12 and 11 mm against the *erg6* mutant and the wild type, respectively. Also, it is worth mentioning that theopederins G-J (**40**–**43**), showed as well antifungal properties against *S. cerevisiae erg6* mutant, but unfortunately no accurate data have been obtained due to the limited isolated quantity (Tsukamoto et al., 1999). Subsequently, Vuong *et al.*, reported that onnamide F (**30**), displayed antifungal effect towards *S. cerevisiae* with LD_{99} value of 1.4 μg/mL (Vuong et al., 2001).

Biosynthesis of pederin and related polyketides

Genome mining (**GM**) has emerged as a powerful biotechnological tool for the discovery of novel marine natural products. With advances in DNA sequencing and bioinformatics, scientists can now analyse the genomes of marine organisms, including bacteria, fungi, and algae, to identify biosynthetic gene clusters (**BGCs**) responsible for the biosynthesis of natural products. By searching for key biosynthetic genes and their associated enzymes, researchers can predict the chemical structures of potential pharmacologically active natural products produced by these organisms.

Moreover, **GM** allows for the identification of biosynthetic pathways that may be responsible for the production of novel bioactive or even non-natural compounds with pharmaceutical or industrial applications. This approach has significantly expanded the scope of marine natural product discovery, enabling the exploration of untapped genetic resources and the discovery of unique molecules from marine organisms.

Additionally, **GM** intriguingly holds great promise for unlocking the vast potential of the marine chemical biodiversity and accelerating the development of new drugs and biotechnological products derived from the marine environment. The biosynthesis of this family of compounds, involves several enzymatic steps. Although the complete biosynthetic pathway has not been fully elucidated, some key reactions and enzymes involved have been identified (Albarano et al., 2020; Bauman et al.,

2021; Chu et al., 2020; Costantini, 2020; Yang et al., 2020).

In 2004, Pie *et al*, were the first to document early biosynthetic steps of the potent toxin and antitumor marine polyketide pederin (**1**). Indeed, the authors successfully identified and isolated a group of potential pederin biosynthesis genes from the metagenome of *Paederus fuscipes* beetles. Through their investigation, they traced these genes back to a bacterial symbiont closely related to *Pseudomonas aeruginosa*.

These genes are responsible for encoding a unique polyketide synthase (**PKS**) non-ribosomal peptide synthetase (**NRPS**) system, known as a mixed modular system. Interestingly, the genes were found to be distributed across two distinct regions of the symbiont genome, which is a rare occurrence when it comes to bacterial secondary metabolites. This discovery sheds light on the fascinating biosynthetic capabilities of these organisms and highlights the complex nature of pederin production (Piel, 2002; Piel et al., 2004b; Piel et al., 2004c).

Structurally, the biosynthetic cascade is complex and intricate process involving multiple enzymatic reactions. The biosynthetic route for such class of compounds for example pederin (**1**) and related compounds like onnamide A (**19**) is believed to start with the assembly of the polyketide backbone. It is hypothesized that a polyketide synthase (**PKS**) enzyme which catalyzes a subsequential iterative condensation of malonyl-CoA units to form a polyketide chain. This process involves the incorporation of various building blocks and modifications, leading to the generation of a highly diverse and complex structure (Kampa et al., 2013).

Following the polyketide chain formation, additional enzymatic transformations occur to introduce and decorate the polyketide core through unique functional groups and create the specific features of pederin (**1**) or onnamide A (**19**). One important step is the installation of the *N*-acyl aminal moiety, which contributes to the compound's bioactivity.

The enzyme responsible for this transformation (**NRPS**) has not been identified, but it is thought to involve the incorporation of an amine and subsequent cyclization to form the *N*-acyl aminal linkage. Further decorations, such as oxidation may occur to generate the final structure of pederin or onnamide A (**19**).

These reactions are likely mediated by a combination of cytochrome P450 enzymes which introduce oxygen atoms (Fig. 1). However, the exact details of each step, particularly the last step which involves extension and adding of arginine amino acid through a sequential of **NRPS** enzymatic reactions are still under investigation. Understanding the biosynthetic pathway of onnamide A (**19**) can provide insights into its production and potentially enable the engineering of biosynthetic pathways for the synthesis of structurally divers analogues with improved properties or therapeutic potential (D'Agostino, 2023; Kampa et al., 2013; Meoded et al., 2018; Piel et al., 2005; Piel et al., 2004a; Rust et al., 2020; Wakimoto, 2023).

Structure activity relationships (SAR)

Most of the compounds in this chemical family exhibit notable cytotoxic activity. However, others display less potent which implies valuable insights into the structure–activity relationships (SAR) within this series of nitrogenous polyketides. As shown in Fig. 2, it illustrates the fundamental aspects of the SAR. Compounds that possess a hemiacetal group instead of an acetal group in the pederin acid unit (C-6) demonstrate lower potency. While the presence of the *N*-Acyl aminal at C-10 enhances potency, but it is not essential for activity, and no discernible advantage is observed when incorporating the *N*-Acyl aminal unit into a ring structure. Intriguingly, compounds containing a methoxy group at C-13 exhibit higher potency compared to those with a hydroxy group, and a loss of activity occurs when the stereochemistry is inverted at this position due to conformational changes in the tetrahydropyran ring. The C-16 side chain demonstrates significant structural variation without significant impact on potency, although increased hydrophobicity in this unit tends to moderately enhance potency, while the presence of OH diminishes potency (Narquizian and Kocienski, 2000a).

Conclusion and future prospective

Marine natural products (**MNPs**) have emerged as a valuable source of bioactive compounds in the field of drug discovery. The diverse and unique marine ecosystem provides an abundance of organisms that produce biologically active compounds with potential pharmaceutical applications. These natural products exhibit a wide range of chemical structures and possess various biological activities, making them attractive candidates for the development of novel drugs. Through advances in rigorous exploration and isolation techniques, researchers

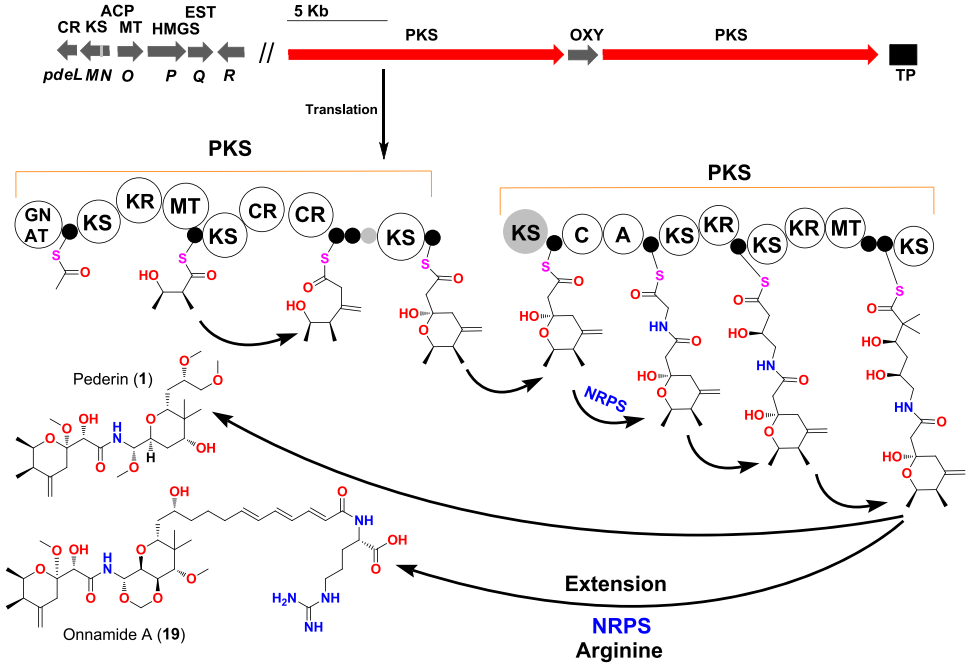

Fig. 1. The protein products of the **PKS-NRPS** genes which play a crucial role in the proposed biosynthetic pathway leading to the production of onnamide and theopederin-type compounds. Each circle depicted in the diagram represents a single domain involved in the process. The intermediates are attached to either an acyl carrier protein (**ACP**) or a peptidyl carrier protein (**PCP**) domain, shown as small-filled circles. Gray domains lack active site motifs and are assumed to be non-functional. Various domains are represented, including **CR** (CR superfamily), EST (esterase), **REG** (regulator), **OXY** (oxygenase), **OR** (oxidoreductase), **TP** (transposase), **C** (condensation domain), **MT** (methyl transferase) and **A** (adenylation domain).

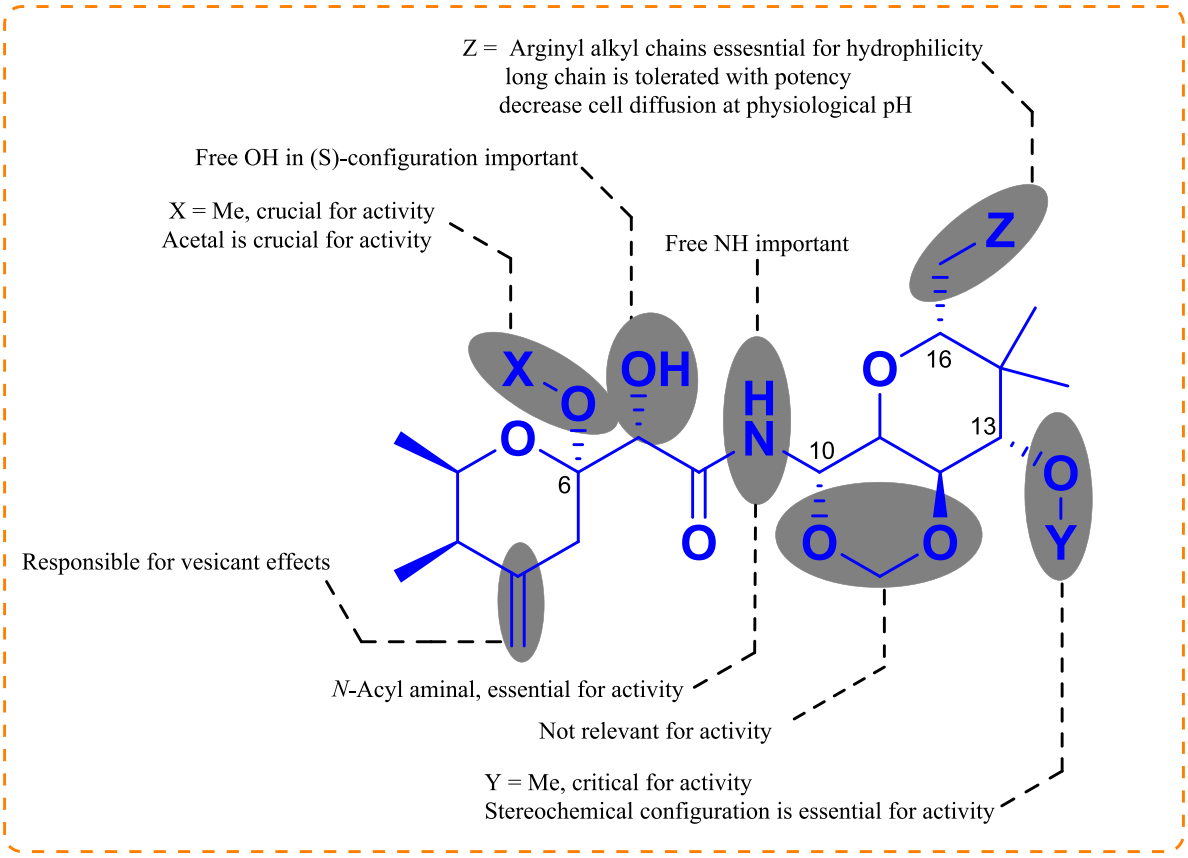

Fig. 2. Fundamental SAR studies of pederin and related molecules.

have successfully identified numerous marine-derived compounds that demonstrate promising therapeutic properties, including anti-cancer, anti-inflammatory, antimicrobial, and neuroprotective activities. Moreover, **MNPs** often exhibit distinct mechanisms of action, making them particularly valuable in combating drug resistance. Despite the challenges associated with the collection and sustainable extraction of marine organisms, advances in technology and research methodologies have enabled scientists to harness the potential of **MNPs** for drug discovery.

As a part of our continuous program to disclose pharmacologically active **MNPs** (El-Demerdash et al., 2021; El-Demerdash et al., 2020; Elgohary et al., 2022; Moriou et al., 2021; Pereira et al., 2023), herein we shed the light on a fascinating group of 36 structurally divers nitrogenous marine polyketide, namely pederins, mycalamides, onnamides, and theopederins.

These distinct families of natural products have garnered significant attention due to their unique structural features and potent biological activities. The activities include anticancer effects against a panel of tumor cell lines. These include murine lymphoma P-388 cells, human promyelocytic (HL-60), colon (HT-29), and lung (A549) cell lines. Other affected cell lines are B 16 melanoma, Lewis lung carcinoma, M5076 ovarian carcinoma, colon 26 carcinoma, and human MX-l (mammary), CX-l (colon), LX-l (lung), and Burkitt's lymphoma tumor xenografts (Burres and Clement, 1989; Fusetani et al., 1992; Matsunaga et al., 1992; Nakamura et al., 2023). The natural products also have antiviral effects against herpes simplex type-l, varicella-zoster virus and polio type-l viruses (Boswell et al., 2023; Perry et al., 1988; Perry et al., 1990; Ul Haq et al., 2023).

Chemically they are characterized by a polyketide-derived core structure comprising two tetrahydropyran rings connected through an *N*-acyl aminal, with various oxidation states decorating the molecule. Therapeutically, these compounds have been classified as potent protein synthesis inhibitors and exhibit potent cytotoxicity, with IC_{50} values below 5 nM in some cases. Such potentiality to inhibit protein synthesis, makes them promising candidates for further investigation in cancer and antiviral therapeutic research. Structurally, the presence of a charged arginyl group like in onnamides may hinder their diffusion into cells at physiological pH, potentially affecting their effectiveness.

Indeed, investigating the structure–activity relationships conducted on the pederin family of antitumor agents provide valuable insights. It has been established that the pharmacophore of these agents lies in the *N*-acyl aminal bridge. Interestingly, the homoallylic acetal array (C4-C6), responsible for the acid lability and vesicant effects of these natural products, is not essential for their antitumor or antiviral activity. The C6 acetal function contributes to the high activity observed in these natural products, although studies with simpler analogues indicate that it is not a necessary component. The presence of a free hydroxyl group at C7, specifically with the (*S*) configuration, is immensely crucial for achieving high activity. Furthermore, the configuration of the aminal centre plays a significant role. The (*S*) configuration at C10 demonstrates significantly higher antitumor activity compared to the (*R*) epimer, whereas compounds with the (*R*) configuration at C10 remain potent antiviral agents. Interestingly, the complex tri-oxadecalin ring system found in mycalamides, onnamides, and theopederins is not essential for high activity (Narquizian and Kocienski, 2000a).

Basically, considering pederin (**1**), the simplest monocyclic structure, is one of the most active natural products in this family. It is closely followed by 18-*O*-methyl-mycalamide B, a synthetic derivative of natural mycalamide B (**14**). Lastly, the side chain at Cl5 shows considerable tolerance for variation without significantly impacting the activity of these compounds. Collectively, these structure–activity investigations shed light on the essential components and pharmacophoric features of the pederin family of antitumor agents. The *N*-acyl aminal bridge, the configuration of the aminal center, the presence of a free hydroxyl group

at C7 with the (*S*) configuration, and the absence of the complex trioxadecalin ring system are all crucial factors in determining their activity. These findings contribute to our understanding of the SAR of these compounds and inform future research and development efforts (Narquizian and Kocienski, 2000b).

Indeed, while significant progress has been made in the field of marine natural product (**MNPs**) drug discovery (Newman, 2023), several challenges still impede the development of **MNPs** drugs. One crucial aspect is ensuring a sustainable supply of these bioactive polyketides. However, considering the existence of reliable and readily available chemical synthetic protocols for many of these marine compounds, along with their structurally related counterparts, provides a promising foundation for conducting extensive *in vitro* and *in vivo* preclinical investigations. This accessibility to synthesized versions of these compounds opens up avenues for researchers to explore their potential through rigorous laboratory studies and animal testing. Such investigations are crucial for evaluating their pharmacological properties, toxicity profiles, and therapeutic potential, ultimately paving the way for their further development as potential drug candidates (Feng et al., 2012; Floreancig, 2014; Jewett and Rawal, 2007; Kellar, 2006; Kocienski et al., 2000; Mosey and Floreancig, 2012; Wu et al., 2011).

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CRediT authorship contribution statement

Mohamed A. Tammam: Writing – review & editing, Writing – original draft, Resources, Investigation. **Amr El-Demerdash:** Writing – review & editing, Writing – original draft, Resources, Investigation, Formal analysis, Validation, Conceptualization.

Declaration of Competing 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.

Data availability

No data was used for the research described in the article.

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