Depsipeptides from Microorganisms: A New Class of Antimalarials

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Abstract: Depsipeptides are a large group of natural products produced by fungi, actinomycetes, cyanobacteria, higher plants and marine organisms. This family of compounds is known to exhibit a wide range of biological activities, and thanks to the progress of isolation techniques and the advances of methods for structure determination, the numbers of depsipeptides having both unique structures and attractive biological activities are increasing. Many of these compounds have shown a wide range of biological activities, and some are in clinical use or have entered human clinical trials as antibiotic or anticancer agents. However, only a handful of them have been evaluated for their antimalarial activity. This paper aims to review the recent advances in depsipeptides as potential antimalarial compounds.

INTRODUCTION

Malaria is one of the most dangerous human parasitic diseases transmitted by four species of protozoa of the genus of *Plasmodium* (*falciparum, vivax, ovale* and *malariae*). They are responsible for more than 500 million malaria cases and 1–3 million deaths each year [1]. *Plasmodium falciparum*, the most virulent of the four species infecting humans, has become resistant to nearly all currently employed antimalarial drugs used for prophylaxis and treatment [2,3].

As infectious diseases evolve and develop resistance to existing pharmaceuticals, terrestrial and marine organisms and microorganisms have proven to be a great source of lead compounds against many of these diseases. Depsipeptides have been reported primarily from invertebrates such as mollusks, sponges, tunicates, bryozoans, from bacteria and cyanobacteria, and from fungi and actinomycetes. In the recent years, many of these compounds have successfully advanced to the late stage of clinical trials [4,5]. The recent renewed interest in the structural characterization of naturally occurring peptides and depsipeptides stems from the recognition that this class of natural products possesses diverse biological activities that may be useful in the development of new therapeutics. Last year alone, Cubist Pharmaceuticals raked in $290 million in sales of cubicin (daptomycin (**1**)), another depsipeptide that has recently joined vancomycin (**2**) on the list of marketed antibiotics [6]. In addition to cubicin, the depsipeptide antibiotic pipeline includes Merck & Co's platensimycin, discovered in soil from South Africa, and Targanta's oritavancin, a semisynthetic glycopeptide licensed from Eli Lilly & Co. [6]. Some depsipeptides such as kahalalide F, hemiasterlin, dolastatins, cemadotin, soblidotin, aplidine and didemnins have recently entered in human clinical trials for the treatment of cancer [5]. However, amongst the huge number of depsipeptides isolated to date, only a handful of them have been tested for their antimalarial activity. Through this review, we aim to highlight the potential of this new class of antimalarials and their possible participation in solving the current malaria control by treatment difficulties encountered in the many malaria endemic countries.

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ANTIMALARIAL DEPSIPEPTIDES

Studies into the antimalarial activity of depsipeptides are still in their early stages especially in comparison to studies concerning their other pharmacological properties such as antibacterial or anticancer. In addition, and as we will fund out during the course of this review, aside from the few papers reporting their isolation and primary evaluation as antimalarials, not much is known on their possible mode of action and, to the best of our knowledge, no structure activity relationship study has been reported in respect to their antimalarial profile.

1. Kahalalides

Kahalalides are a series of marine depsipeptides many of which have been isolated from the marine mollusk *Elysia rufescens* [7-10]. However, it was later discovered that a green alga, *Bryopsis* sp., on which the mollusk feeds is also a source of kahalalide F, but at lower concentration than found in the mollusk [8]. Kahalalide D is the smallest of this class of depsipeptides and serves as a model for structure elucidation of all the others. Structurally, it consists of three amino acids (*L*-arginine, *L*-proline and *D*-tryptophan), and the *β*-hydroxy group of its fatty acid portion (3-hydroxy-7-methyloctanoic acid) furnishes the ester linkage of the depsipeptides cycle. Next in size are kahalalides A, B, C and E, with either six (C and E) or seven (A and B) amino acid residues. In kahalalide A (**3**), the ester linkage arises from the carboxyl of serine and the hydroxyl of the second threonine, with 2-methylbutyric acid, which form an amide with one of the phenylalanine, constituting its fatty acid portion. Kahalalide G is the only acyclic compound of the series, with the ester linkage between the carboxyl of the terminal valine and the hydroxyl of terminal threonine missing.

The biological activities of many of the kahalides have been reported. Kahalalide F (the largest of the *Elysia* depsipeptides) displayed significant *in vitro* and *in vivo* antitu-

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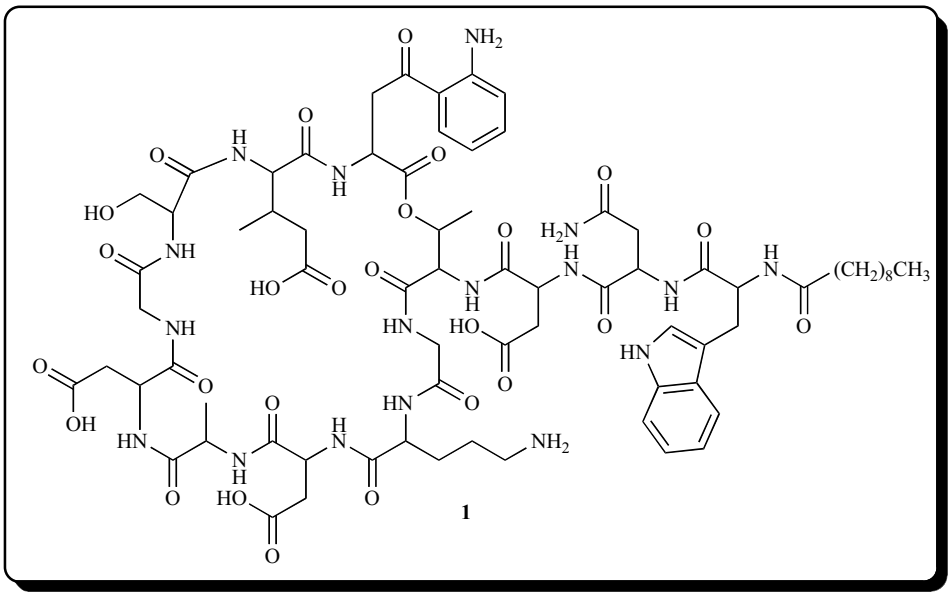

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mor activity in various solid tumour models, including colon (HT-29), breast (T-47D), non-small-cell lung (A-549), and prostate (DU-145) cancers [11]. This compound has been investigated in phase I clinical trials for androgen-refractory prostate cancer [12], and in phase II clinical studies with patients having liver or non-small-cell lung cancer, and melanoma [13]. Recently, the results of the aforementioned phase II clinical study of kahalalide F have been reported, revealing an excellent tolerability with no serious adverse events [14]. The mechanism of action of Kahalide F is unclear. It has been shown to induce cell swelling and blebbing in two hepatoma cell lines [15], to increase membrane permeability to cationic PI and large molecules, in addition to the disruption of lysosomes [16]. ErbB3 has also been highlighted as a possible target for kahalide F along with an inhibition in Akt signalling [17].

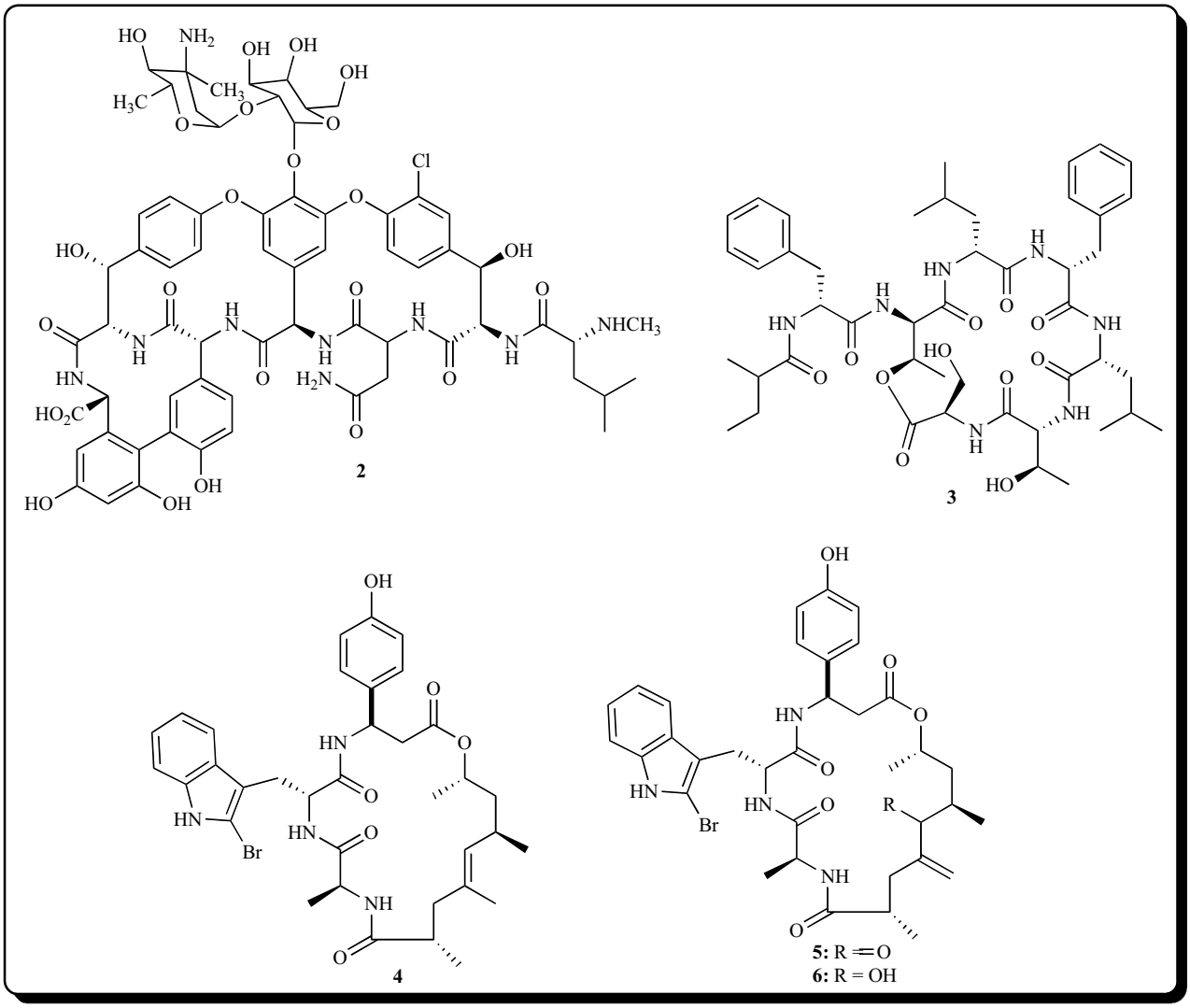
However, only kahalalide A (**3**) is reported to possess modest antimalarial activity against *P. falciparum* (IC_{50} 11 μM) [8]. This compound that has also displayed antimycobacterial activity against *Mycobacterium tuberculosis* (83 % growth inhibition at 14 μM) [18,19] does not have significant homology to kahalalide F. Thus, it is not cytotoxic to various tumor cell lines [19], suggesting a selective antimalarial and antibacterial activity. The total synthesis of kahalalide A was achieved by solid-phase [18], a route that can be adapted for the preparation of analogues for a deeper investigation of their antimalarial properties.

2. Jaspamides

After the discovery of the cyclic depsipeptide jaspamide (**4**) (jasplakinolide) in the sponge *Jaspis johnstoni* in 1986 [20-22] several other reports of the isolation of the same compound from other sponge genera, including *Auletta constricta* [23] and *Hemiasterella minor* [24], appeared in the literature. Later on, jasplakinolide B was reported from *Jaspis johnstoni* [25], and jaspamides B (**5**) and C (**6**) from *Jaspis splendans* [26]. Structurally, these compounds are commonly constituted by two main portions: the tripeptide portion comprising (*R*)-*β*-tyrosine, (*S*)-alanine and *N*-methylbromoabrine residue, and the aliphatic carboxylic portion consisting of the 8-hydroxynonenoic acid unit. However, only jaspamide (jasplakinolide (**4**)) has been reported for its antimalarial properties [27].

Jasplakinolide is known to induce actin polymerisation and stabilize the filaments. Actin filaments are involved in cell motility, cell invasion, phagocytosis amongst other processes. The mechanisms by which jasplakinolide stabilises actin are: (i) lowering the critical number of subunits required for polymerisation; (ii) releasing actin from sequestering proteins; (iii) binding to and stabilising filaments [28]. Experiments with *Toxoplasma gondii*, another apicomplexan parasite often used as a model for *Plasmodium* sp, have shown that jasplakinolide inhibits cell invasion and causes the formation of an apical protrusion by redistribution of actin filaments [28]. There has been some confusion over whether jasplakinolide causes a decrease or an increase in motility. However, work by Wetzel *et al.* has since shown that jasplakinolide at low concentrations increases motility, but in a manner which is unproductive to the parasite [28].

The effect of jasplakinolide on the growth, invasion, and actin cytoskeleton of *P. falciparum* had been examined. Jasplakinolide markedly decreased the parasitemia in a synchronized culture of *P. falciparum* strain FCR-3 in a time- and concentration-dependent manner [27]. The decrease became evident at day 2 at concentrations of 0.32 μM and above, and parasites are cleared at day 4. Giemsa-stained smears of *P. falciparum*-infected erythrocytes demonstrated that there was no effect on the development of schizonts from ring forms [27]. Merozoites were released from the infected erythrocytes in a normal manner with and without jasplakinolide. However, there were no ring form-infected erythrocytes when jasplakinolide was administered, even after the release of merozoites [27]. This indicates that the merozoites exposed to jasplakinolide failed to invade erythrocytes. The inhibitory effect of jasplakinolide on the parasitemia was reversed by the removal of the drug after exposure to 1.0 μM of jasplakinolide for 1 day. Electron microscopy revealed that the merozoites treated with jasplakinolide



showed a protrusion of the apical end which contained the microfilament structure, while immunoblot analysis indicated that the jasplakinolide treatment increased F-actin filaments of merozoites but had no effect on those of the trophozoites and schizonts [27]. Additionally investigations involving *P. berghei* ookinetes and jasplakinolide have shown that, at low concentrations, uncoordinated motility is observed, with an absence of motility at high concentrations [29].

It is important to mention that the total synthesis of jasplakinolide has been achieved by several research groups [30-32], and some simplified analogues have been prepared for the investigation of their anticancer properties [33]. These achievements can be very helpful for further investigation of the antimalarial activity of this compound, and might help build a structure activity relationship profile as well.

3. Paecilodepsipeptides

Paecilodepsipetide A (**7**), together with its linear analogues paecilodepsipeptides B (**8**) and C (**9**), were isolated from the insect's pathogenic fungus *Paecilomyces cinnamomeus* BCC 9616 by Isaka *et al.* [34]. The unique structural feature of paecilodepsipeptide A is that it is constituted of five amino acid residues amongst which three *D*-amino acids, including the unusual *O*-prenyl-*D*-tyrosine, and only one *L*-amino acid (alanine), with the fifth amino acid being glycine. The ester linkage of the depsipeptides cycle arises through a coupling between the hydroxyl group of the 2-hydroxycarboxylic acid residue shown to be 3-phenyllactic acid, and the carboxyl of the *O*-prenyltyrosine. The linear analogues (**8** and **9**) are the hydrolysis and methanolysis derivatives of paecilodepsipeptide A (**7**).

Amongst these three compounds, only paecilodepsipeptide A exhibited activity against *P. falciparum* K1 strain, with an IC_{50} value of 4.9 μM. This compounds also showed cytotoxicity to two cancer lines KB (IC_{50} 5.9 μM) and BC (IC_{50} 6.6 μM), with no toxicity to Vero cells (African green monkey kidney fibroblasts) even at a concentration of 67 μM [34]. Linear analogues were shown to be inactive in both assays, suggesting the importance of the cyclic depsipeptides structure for the biological activities [34].

4. Pullularins

Pullularins A-D (**10-13**) are another series of cyclohexadepsipeptides isolated from endophytic fungus *Pullularia* sp.

BCC 8613. Structurally speaking, pullularins A-D vary not only in the substitution patterns of the amino acids, but also the amino acids themselves. However two structural features are consistent across them: a (*S*)-*O*-prenyltyrosine unit and a combination of (*S*)-proline and (*R*)-2-hydroxy-3-phenylpropionic acid. They have been subjected to several biological assays including antimalarial, antitubercular, antiviral and cytotoxicity [35]. Pullularins A (**10**), B (**11**) and C (**12**) were found to possess attractive antimalarial activity, with IC_{50} values of 4.6, 4.2 and 13 μM, respectively, with little or no toxicity to Vero cells and KB, BC and NCI-H187 cancer cell lines [35].

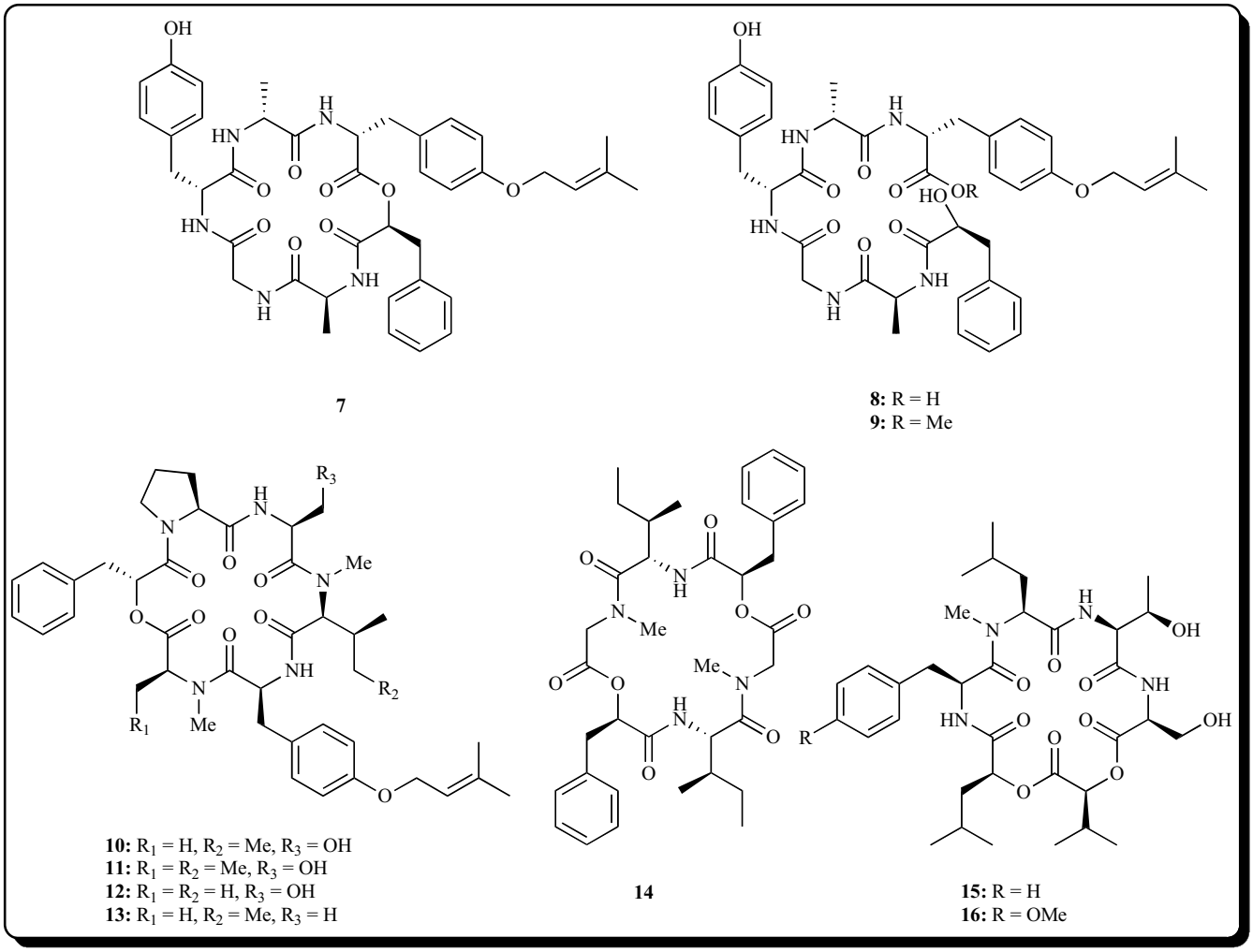
5. Hirsutellide A and Hirsutatins

Hirsutellide A (**14**) and hirsutains A (**15**) and B (**16**) have been isolated from fungi of the *Hirsutella* family. Hirsutellide A was isolated from entomopathogenic fungus *Hirsutella kobayassi* BCC 1660 [36], while hirsutatins A and B were isolated from *Hirsutella nivea* [37]. The interesting structural feature of hirsutellide A is that it has a 2-fold rotational plane of symmetry, as it consists of two identical tridepsipetides. Each of these tridepsipetides is comprised of three subunits, 2-hydroxy-3-phenylpropanoic acid, *N*-methylglycine and isoleucine, identically disposed. As for hirsutatins A and B, they vary only in that the phenylalanine of hirsutatin A is replaced in hirsutatin B by a 4'-methoxytyrosine residue. The three remaining amino acid residues are *N*-methyl-*L*-leucine, *L*-threonine and *L*-serine, with two 2-hydroxycarboxylic acid residues consisting of *L*-2-hydroxyisovaleric acid and *L*-2-hydroxyisocaproic acid.

Hirsutellide A has displayed antimalarial activity against K1 strain of *P. falciparum*, with an IC_{50} value of 4.2 μM [36], while amongst hirsutatins A and B, only hirsutatin B exhibited antimalarial activity, with IC_{50} value of 8.2 μM [37]. Hirsutatins A was inactive even at a concentration of 30 μM and none of the three compounds were toxic to Vero cells [36,37]. The total synthesis of hirsutellide A has been achieved by Xu *et al*. [38], rending possible a structure activity relationship study and optimization of its antimalarial activity.

6. Beauvericins and Allobeauvericin

Beauvericin (**17**), a cyclohexadepsipeptide antibiotic consisting of three *L*-*N*-methylphenylalanine units connected alternatively with three *D*-2-hydroxyisovaleric acid residues has commonly been isolated from *Beauveria bassiana* [39] and several fungi [40-44]. Beauvericin is also an insecticide, toxic to mosquito larvae [39,40], brine shrimp [39], blowfly [45] and Colorado potato beetles [40]. The same compound has also displayed anti-convulsion, anti-arrhythmia, sedation



and anti-tumor activities [46]. Gupta *et al.* had isolated two minor analogs, beauvericins A (**18**) and B (**19**), possessing one and two 2-hydroxy-3-methylpentanoic acid residues, respectively, instead of *D*-2-hydroxyisovaleric acid, as minor metabolites, from *B. bassiana* [47]. Recently, beauvericin and beauvericin A were also reported from *Paecilomyces tenuipes* BCC 1614, an insect's pathogenic fungus [48], and together with beauvericins B and C (**19-20**), and allobeauvericins A-C (**21-23**), their antiplasmodial activity was evaluated against the K1 strain of *P. falciparum* [48,49]. All the tested compounds displayed attractive antimalarial activity: beauvericin (IC_{50} 1.7 μM), beauvericins A (IC_{50} 2.3 μM) and B (IC_{50} 2.8 μM), allobeauvericins A (IC_{50} 2.5 μM), B (IC_{50} 3.0 μM) and C (IC_{50} 1.9 μM) [49]. However, these compounds were also very toxic to the Vero cell suggesting that their antimalarial activity might be related to their cytotoxic behaviour.

7. Enniatins

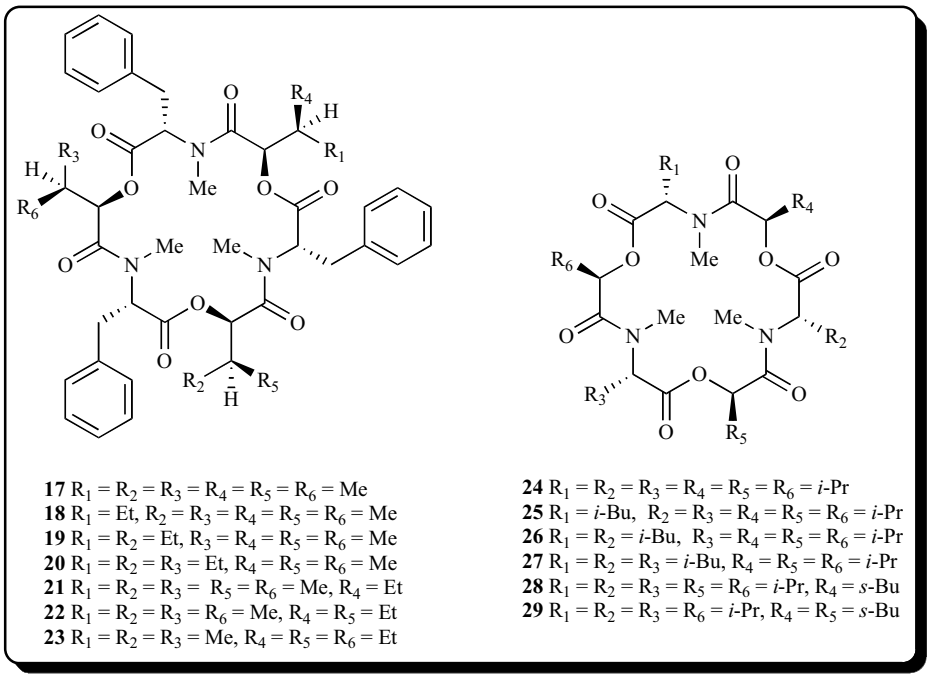
Enniatins are also a well-known cyclohexadepsipeptide class of antibiotics produced by various *Fusarium* species [50-54]. They consist of three *L*-*N*-methylamino acids and three *D*-2-hydroxyisovaleric acid residues linked alternatively to furnish an 18-membered cyclodepsipeptide structure. Several isomers of enniatins possess different substituents on the three *L*-*N*-methylamino acid residues. However, they usually have fixed substructure at the *D*-2-hydroxycarboxylic acid residue ($R_4 = R_5 = R_6 =$ *i*-Pr). Enniatins H and I are two isomers bearing one and two 2-hydroxy-3-methylpentanoic acid residues, respectively, instead of *D*-2-hydroxyisovaleric acid. They were identified, together with enniatins A and B (**24**), as minor metabolites from the insect's pathogenic fungus *Verticillium hemipterigenum* [55].

This class of compounds have been shown to exhibit antibiotic [51, 52, 56], insecticidal [45, 53] and phytotoxic [54, 57] activities, and also inhibit acyl-CoA; cholesterol acyltransferase (ACAT) [58]. The antimalarial activity of enniantins B (**24**), B_4 (**25**), C (**26**), G (**27**), H (**28**) and I (**29**), were evaluated against the K1 strain of *P. falciparum*, and all the tested compounds displayed strong properties: enniantins B (IC_{50} 0.42 μM), B_4 (IC_{50} 0.31 μM), C (IC_{50} 1.6 μM), G (IC_{50} 0.67 μM), H (IC_{50} 2.9 μM) and I (IC_{50} 0.36 μM) [55]. It should be mentioned that these compounds also exhibited cytotoxicity activities, but these were rather weak compared to their antimalarial activity. They also displayed slight toxicity against Vero cells (see Table **1**).

PERSPECTIVES

Due to their relative structural complexity and the limited quantity generally isolated from natural sources, many depsipeptides are primarily investigated for their antitumor/anticancer activities. Thus, this family of compounds is generally regarded as cytotoxic entities, and this have overshadowed their other biological properties. However, as we have already mentioned, the antibiotic [51-52, 56], antifungal [40-44], insecticidal [39-40, 45, 53, 45], phytotoxic [54, 57], anti-convulsion, anti-arrhythmia and sedative [46] activities of depsipeptides have also been intensively investigated. The marketed antibiotic Fusafungine (Licabiosol®), which is a combination of several anniatins, possess bacteriostatic activity against most microorganisms responsible for the respiratory tract infections [59]. Moreover, the broad-spectrum depsipeptide antibiotic, vancomycin, is currently the only approved treatment for *Clostridium difficile* infection [6].

The antimalarial potential of depsipeptides is real, at least for cyclic depsipeptides. Many of them have displayed antimalarial activity at the low micro-molar range, with selectivity indexes ranging from 2 to 158 (Table **1**). To the best of our knowledge, the only reported linear depsipeptides (paecilodepsipeptides B and C) evaluated for their antimalarial activity were inactive [34]. However, as investigations into the antimalarial activity of this family of compounds are still



17 $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 =$ Me
18 R_1 = Et, $R_2 = R_3 = R_4 = R_5 = R_6$ = Me
19 $R_1 = R_2$ = Et, $R_3 = R_4 = R_5 = R_6$ = Me
20 $R_1 = R_2 = R_3$ = Et, $R_4 = R_5 = R_6$ = Me
21 $R_1 = R_2 = R_3 = R_5 = R_6$ = Me, R_4 = Et
22 $R_1 = R_2 = R_3 = R_6$ = Me, $R_4 = R_5$ = Et
23 $R_1 = R_2 = R_3$ = Me, $R_4 = R_5 = R_6$ = Et

24 $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 =$ *i*-Pr
25 R_1 = *i*-Bu, $R_2 = R_3 = R_4 = R_5 = R_6$ = *i*-Pr
26 $R_1 = R_2$ = *i*-Bu, $R_3 = R_4 = R_5 = R_6$ = *i*-Pr
27 $R_1 = R_2 = R_3$ = *i*-Bu, $R_4 = R_5 = R_6$ = *i*-Pr
28 $R_1 = R_2 = R_3 = R_5 = R_6$ = *i*-Pr, R_4 = *s*-Bu
29 $R_1 = R_2 = R_3 = R_6$ = *i*-Pr, $R_4 = R_5$ = *s*-Bu

Table 1. Summary of the Antimalarial Activity of Depsipeptides and their Selectivity

Antimalarial Depsipeptides	Plasmodium IC_{50} (μM)	VERO Cell IC_{50} (μM)	Selectivity Index	References
Kahalalide A (**3**)	11	NA	-	[8]
Jasplakinolide (**4**)	0.32	NA	-	[27]
Paecilodepsipeptide A (**7**)	4.9	67	14	[34]
Pullularin A (**10**)	4.6	46	10	[35]
Pullularin B (**11**)	4.2	> 63	> 15	
Pullularin C (**12**)	13	> 66	> 5	
Hirsutellide A (**14**)	4.2	> 75	> 18	[36]
Hirsutatin B (**16**)	8.2	> 71	> 9	[37]
Beauvericin (**17**)	1.7	13	8	[49]
Beauvericin A (**18**)	2.3	11	5	
Beauvericin B (**19**)	2.8	11	4	
Allobeauvericin A (**21**)	2.5	7.4	3	[49]
Allobeauvericin B (**22**)	3.0	5.4	2	
Allobeauvericin C (**23**)	1.9	6.3	3	
Enniatin B (**24**)	0.42	27	64	[55]
Enniatin B_4 (**25**)	0.31	28	90	
Enniatin C (**26**)	1.6	> 75	> 47	
Enniatin G (**27**)	0.67	66	99	
Enniatin H (**28**)	2.9	58	20	
Enniatin I (**29**),	0.36	57	158	

NA= Non-available; Selectivity index = IC_{50} against Vero cells / IC_{50} against *P. falciparum.*

embryonic when compared to their other pharmacological properties, such as anticancer or antibiotics, others antimalarial classes of cyclic or even linear depsipeptides may still be uncovered. The modulation of their antimalarial activity as well as their cytotoxicity is probably governed by their individual lipophilic properties designated by their different substitution patterns. This can be easily observed when compared allobeauvericin B (**22**) (IC_{50} 3.0 μM, selectivity index = 2) and enniatin I (**29**) (IC_{50} 0.36 μM, selectivity index = 158), two compounds having the same basic skeleton, and different only by their substitution patterns, with enniatin I (**29**) obviously more lipophilic than allobeauvericin B. This is important as it indicates that careful designing using appropriate substitutions on the depsipeptides skeleton can lead to new effective and save antimalarial drugs. Consequently, depsipeptides represent excellent target compounds for structure activity relationship studies and possible optimization of their antimalarial properties for chemotherapy.

Many of the biological activities of depsipeptides have been proposed to be related to their ionophoric properties [60] and their capacity for translocating metal cations without formation of pores through biological and/or bilayer membranes [61-63]. Enniatins are known to uncouple oxidative phosphorylation in isolated mitochondria, a reaction mediated by induction of an energy dependent accumulation of potassium ions [64]. Enniatins D, E and F were also found to be potent inhibitors of mammalian cholesterol acyl transferase (ACAT) [58]. As some of these proteins, enzymes and pathways are present in *Plasmodium* species, they represent potential target for antimalarial depsipeptides. However, only radio and/or photoaffinity labeling studies can definitely identify their putative drug targets, an imperative step in the understanding of their possible mechanism of action. It is only through these different steps that antimalarial depsipeptides could have a chance to make it to a usable drug, and we believe that there is enough room for them in this area of antimalarial drug discovery where fighting resistance is a perpetual challenge.

CONCLUSION

The development of new antimalarial treatments should give critical consideration to the economics of drug development and delivery as most companies restrain from active research in antimalarials, and this area has became basic-science oriented involving only academics. This holds inherent organisational and financial difficulties in maintaining a systematic and sustainable research structure for the development of new drugs. This is the direct consequence of the fact that malaria is one of the many neglected diseases, and is endemic only in the poorest areas of the world. In this respect, the limited quantities of depsipeptides that are often

isolated from natural sources, coupled to their tedious synthetic accessibility (several steps reactions that lead to very low over all yields) are potential drawbacks to this family of compounds as antimalarials. However, we should not underestimate what the structure activity relationship studies and the investigation of the drug target as well as the possible mechanism of action of this newly uncovered antimalarial family of compounds could bring in term of the better understanding of the biology and biochemistry of the parasite. Moreover, is not the main goal of structural optimization that to prepare analogues that maintains or even improves the activity while removing the unnecessary complexity of the molecule? Thus, some optimized analogues could be very potent and easily accessible. It is then worthy that this family of compounds should be given serious and careful investigations for their antimalarial potential.

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