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Potential of *Streptomyces* in producing antiplasmodial lead compounds

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ABSTRACT: *Streptomyces* are bacteria of great importance for several decades. Numerous potent metabolites characterized as antibiotics including macrolides and polypetides have been reported from *Streptomyces* and developed as effective drugs for the treatment of several illnesses. Therefore, *Streptomyces* can be considered as an important source of bioactive compounds which might help in the eradication of malaria which remains one of the greatest threats to human life, especially in the tropical and sub-tropical regions. The reported *in vitro* antiplasmodial properties of chemical constituents from *Streptomyces* strains have led to promising results like bafilomycin A1 (**9**), concanamycin A (**10**), elaiophylin (**17**), cyclomarin C (**23**), urdamycinone E (**44**), geldanamycin (**52**) and metacycloprodigiosin (**74**) which individually exhibited strong antiplasmodial activity against the chloroquine-resistant strain *Plasmodium falciparum* K1 with IC_{50} values of 0.041 μg/ml, 0.2 nM, 0.22 μg/ml, 0.24 μg/ml, 0.0534 μg/ml, 0.35 μg/ml and 0.0050 μg/ml, respectively. In some cases, the tested compound was most active than the reference and without observed toxicity until the highest concentration. However, more *in vivo* and toxicity studies are necessary for further guidance in the process of drug development. To the best of our knowledge, no specific review has been done on the potential of *Streptomyces* in furnishing antiplasmodial compounds for malaria control. This paper aims to compile the literature up to 2021 on antiplasmodial compounds isolated from *Streptomyces* for easy and rapid access to the literature for further investigations in continuity.

1. INTRODUCTION

The last report of the World Health Organisation (WHO) on malaria worldwide indicates that there was an increased case incidence of malaria between 2020 and 2021 due to the disruption to services during the Covid-19 pandemic with almost 241 million malaria cases and 627,000 deaths in 85 malaria-endemic countries (WHO, 2021). This observation supports that malaria is still among the most harmful parasitic diseases and a major public health problem in several tropic and subtropic regions of the world, especially the developing countries which are poorly deserved with equipped medical centres and where the resistance of *Plasmodium falciparum* to the prescribed antimalarial drugs have been reported (Nasomjai et al., 2014; Ogbole et al., 2018). *Plasmodium falciparum* is the most virulent parasite that causes the most severe forms of malaria and the highest rate of mortality with children and pregnant women as the most affected people (Júnior et al., 2012). Several strategies have been proposed by WHO in preventing and curing the diseases over the last decades, including the combination of effective therapeutic agents like artemisinin-based combination therapy (ACT), the large distribution of long-lasting insecticide-treated bed nets or the development of new insecticides to eliminate its malaria mosquito vectors (Happi et al., 2015, 2022). However, new more potent antimalarial drugs are needed to supply the ones existing already and address the observed resistance (Bathurst & Hentschel, 2006). Until 2006, four main classes of compounds have been identified among the most prescribed antimalarial drugs: The quinine derivatives like chloroquine, mefloquine, amodiaquine or the aminoquinolines like primaquine; the antifolate compounds like pyrimethamine, dapsone or sulfadoxine, the artemisinin derivatives like artesunate, artemether or co-Artem; and finally the hydroxynaphthoquinone like atovaquone (Baniecki et al., 2007). In this regard for new antiplasmodial drug discovery, it seems imperative to explore new sources of bioactive metabolites

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with new structural diversity to increase the opportunities in structure modifications as well as in the development of a high number of possibilities of active compounds.

The bacteria called *Streptomyces* represent an interesting source of specialized metabolites with a high structural diversity and a large scale of biological activities. It is well reported that mostly produced antibiotics like chloramphenicol from *Streptomyces venezuelae* and used in the treatment of typhoid, rifampicin and vancomycin from *S. mediterranei* and *S. orientalis*, respectively, and which have been important antibiotics prescribed in the treatment of leprosy and methicillin-resistant *Staphylococcus aureus*, respectively (Chater, 2006). Many of these antibiotics derived from *Streptomyces* are highly functionalised compounds that mostly belong to the class of macrolides or cyclopolypeptides. Like other microorganisms (fungi or bacteria) which live in their hosts (Happi et al., 2015), *Streptomyces* can be isolated from plant material, soil or marine sources like sea plant, sea sediment or sea animals. Our literature survey provided us with significant data on the high structural diversity and strong activity of some *Streptomyces* compounds compared to the well-known standard drugs and which deserve further attention in the development of new potent antimalarial drugs. To the best of our knowledge, no review article has been published on the phytochemistry and pharmacology of the bacteria *Streptomyces* for their contribution in fighting against malaria as a source of antiplasmodial agents. This review covers the documented works up to December 2021.

2. METHODOLOGY

This paper has been written based on collected data previously reported in the literature over the last decades up to 2021. Numerous online libraries including Scifinder and Scifinder^n, PubMed, Google Scholar as well as Web of Science were used in searching for information on antiplasmodial metabolites from *Streptomyces*. The keywords *Streptomyces*, *Plasmodium*, antiplasmodial and malaria were used to monitor and refine our search without language restriction.

3. ANTIPLASMODIAL LEAD COMPOUNDS FROM *STREPTOMYCES*

The literature survey on the previous chemical and pharmacological studies of *Streptomyces* revealed that numerous specialized metabolites, which are mostly antibiotics, have been isolated from an important number of strains that were not fully identified in many cases but reported as *Streptomyces* sp. and their original strain codes from the authors' databank. The reported *Streptomyces* sp. have been isolated from plant material like rice (Supong, Thawai, et al., 2016), from marine source (Buedenbender et al., 2018; Supong et al., 2012) or from soil (Intaraudom et al., 2015; Supong, Sripreechasak, et al., 2016). Among the reported compounds from *Streptomyces*, 70 distinct compounds have demonstrated an antiplasmodial potency including 51 natural products (~72.9 %) and 19 synthetic derivatives (~27.1 %) prepared from isolated natural products. The 51 natural occurring antiplasmodial compounds from *Streptomyces* can be organized into thirteen different classes of specialized metabolites sorted as follows: Macrolides were the most abundant (~23.5 %) followed by anthraquinones (~15.7 %), polypeptides (~11.7 %), geldanamycin analogues (~7.8 %), pactamycin analogues, polyether compounds and diketopiperazines (~5.9 %, each), cyclopeptides and carbazomycin analogues (~3.9 %, each), sesquiterpenoid, diterpenoid and zeatin-type compound (~2.0 %, each) and others (~9.8 %). As we recently reported, a pure compound should exhibit an $IC_{50} \leq 10\ \mu M$ to be considered as an active compound by the industry (Happi et al., 2022).

Furthermore, the seventy reported antiplasmodial compounds from *Streptomyces* have been tested against a total of eight *Plasmodium falciparum* strains including four chloroquine-sensitive strains (*P. falciparum* 3D7, D6, NF54 and HB3) and four chloroquine-resistant strains (*P. falciparum* K1, Dd2, W2 and 7G8) (Table 1). Globally, the resistant strains K1, Dd2 and the sensitive strain 3D7 have been the most used during the antiplasmodial tests of *Streptomyces* compounds. Thus, the promising results against the resistant strains indicated that *Streptomyces* can be an important source of active principles to handle the resistance of *P. falciparum* which represent the main issue in controlling the progress and the eradication of malaria (Happi et al., 2022). Artemisinin (**1**) and its derivatives dihydroartemisinin (**2**) and artesunate (**3**), as well as the gold antimalarial drug chloroquine (**4**) and other standard drugs like mefloquine (**5**), puromycin (**6**), pyrimethamine (**7**) and pyronaridine (**8**), have been used as reference compounds (standards) during the reported investigations (Figure 1). Their potencies against the used strains of *P. falciparum* are compiled in Table 1.

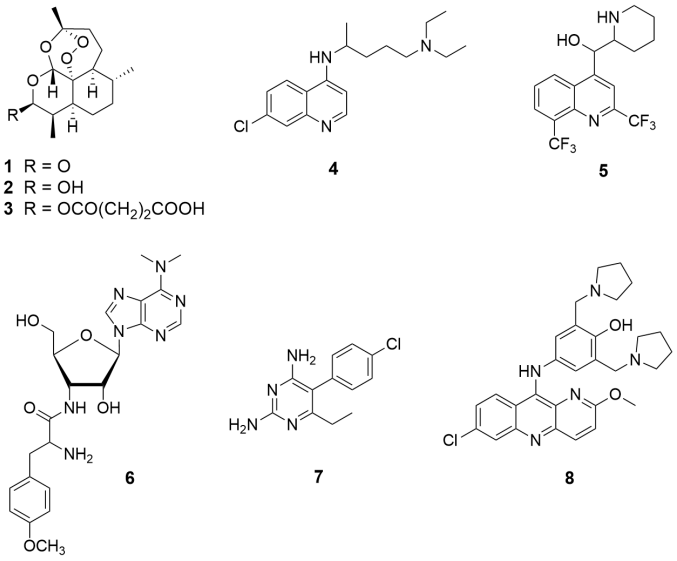


Figure 1. Some drugs used as standard for antiplasmodial tests.

The reported active compounds from *Streptomyces* can be classified into five categories based on their potencies in comparison with the criteria for antiplasmodial activity against *P. falciparum* used by the World Health Organization that

Table 1
Potencies of standard drugs used during the recorded antiplasmodial tests.

Type of *P. falciparum*	Strains index	Standard, IC_{50}	Reference
	3D7	Artesunate (**3**), 0.9 nM	Kiefer et al. (2019)
		Chloroquine (**4**), 3.4 nM	Buedenbender et al. (2018)
		Dihydroartemisinin (**2**), 0.4 nM	
		Puromycin (**6**), 148.9 nM	
CQ-sensitive strains		Pyrimethamine (**7**), 4.7 nM	
		Pyronaridine (**8**), 7.4 nM	
	D6	Chloroquine (**4**), 10.6 nM	Almabruk et al. (2013)
	NF54	Chloroquine (**4**), 6 nM	Happi et al. (2015)
	HB3	Chloroquine (**4**), 9.47 nM	Baniecki et al. (2007)
		Mefloquine (**5**), 9.63 nM	
		Artemisinin (**1**), 9.70 nM	
	K1	Artemisinin (**1**), 3.9 nM	Isaka et al. (2002)
		Chloroquine (**4**), 0.46 uM	Jang et al. (2017)
		Dihydroartemisinin (**2**), 1.98 nM	Intaraudom et al. (2015)
		Mefloquine (**5**), 29.1 nM	Supong, Thawai, et al. (2016)
	Dd2	Artesunate (**3**), 1.3 nM	Buedenbender et al. (2018)
CQ-resistant strains		Chloroquine (**4**), 87.9 nM	
		Dihydroartemisinin (**2**), 0.6 nM	
		Puromycin (**6**), 114.4 nM	
		Pyronaridine (**8**), 8.3 nM	
	7G8	Chloroquine (**4**), 89.5 nM	Almabruk et al. (2013)
	W2	Chloroquine (**4**), 70 nM	Mackinnon et al. (1997)

CQ: chloroquine

indicates that : Pronounced activity (IC_{50} < 5 μg/ml or IC_{50} $\leq$ 0.1 μM) ; good activity (5 < IC_{50} <10 μg/ml or IC_{50} > 0.1 μM but $\leq$ 5 μM); moderate activity (10 < IC_{50} < 20 μg/ml or IC_{50} > 5 μM but < 20 μM) ; low activity (20 < IC_{50} < 40 μg/ml or IC_{50} > 20 μM but < 50 μM) and inactive if IC_{50} > 40 μg/ml or IC_{50} > 50 μM (WHO 2022;) (Happi et al., 2022).

3.1. Macrolides

Macrolides represent an important class of antibiotics isolated from microorganisms including the most famous ones azithromycin and erythromycin which are pharmaceutical drugs available on market. Through the last decades, the chemical investigations of several *Streptomyces* strains led to the isolation and characterization of a number of macrolides including nineteen which were identified as potent antiplasmodial agents according to the data available in the literature so far (Table 2, Figure 2).

Earlier in 2002, the bacterial strain *Streptomyces spectabilis* BCC4785 has been isolated from the soil sample and the bio-guided fractionation of its extract led to the isolation of the macrolide bafilomycin A1 (**9**) showing a significant activity (IC_{50} = 0.041 μg/ml) against *Plasmodium falciparum* K1 (Isaka et al., 2002). Later in 2006, another macrolide named concanamycin A (**10**) from *Streptomyces* sp. displayed a strong antiplasmodial activity supported by its IC_{50} of 0.2 nM against *P. falciparum* K1 (Auparakkitanon & Wilairat, 2006). Two 20-membered macrolides samroiyotmycins A (**11**) and B (**12**) were reported from *Streptomyces* sp. BCC33756 and tested for their antiplasmodial potency which gave the IC_{50} values of 3.65 μg/ml and 3.16 μg/ml, respectively, against *P. falciparum* K1 (Dramae et al., 2013).

In 2016, Supong and co-workers have isolated the strain BCC72023 of *Streptomyces* sp. from *Oryza sativa* (rice). Its screening for antiplasmodial compounds gave the identification of three macrolides namely efomycin M (**13**) reported for the first time from a natural source, efomycin G (**14**) and oxohygrolidin (**15**) which displayed interesting potency against *P. falciparum* K1 with IC_{50} values of 5.23 μg/ml, 2.37 μg/ml and 2.30 μg/ml, respectively (Supong, Thawai, et al., 2016). Within the same year, the same authors reported five additional macrolides from the terrestrial *Streptomyces* sp. BCC71188 including monoglycosylelaiolide (**16**), elaiophylin also called azalomycin (**17**), 11,11′-odimethylelaiophylin (**18**), oxohygrolidin (**19**) and the previously-reported efomycin G (**14**) which displayed significant antiplasmodial activity against *P. falciparum* K1 with IC_{50} values of 2.46 μg/ml, 0.22 μg/ml, 1.47 μg/ml, 2.30 μg/ml and 2.37 μg/ml, respectively (Supong, Sripreechasak, et al., 2016).

Most recently in 2018, elaiophylin (**20**) has been reported from *Streptomyces* sp. USC-16018 with an IC_{50} of 777.9 nM with 96.6% inhibition at 40 μM against the chloroquine-sensitive strain *P. falciparum* 3D7 while it showed a more relevant activity against *P. falciparum* Dd2 with an IC_{50} of 598.5 nM with 86.1% inhibition at 40 μM (Buedenbender et al., 2018).

Furthermore, six macrolides have been partially characterized as high functionalized compounds which showed interesting antiplasmodial activity. Briefly, munumbicins A–D isolated

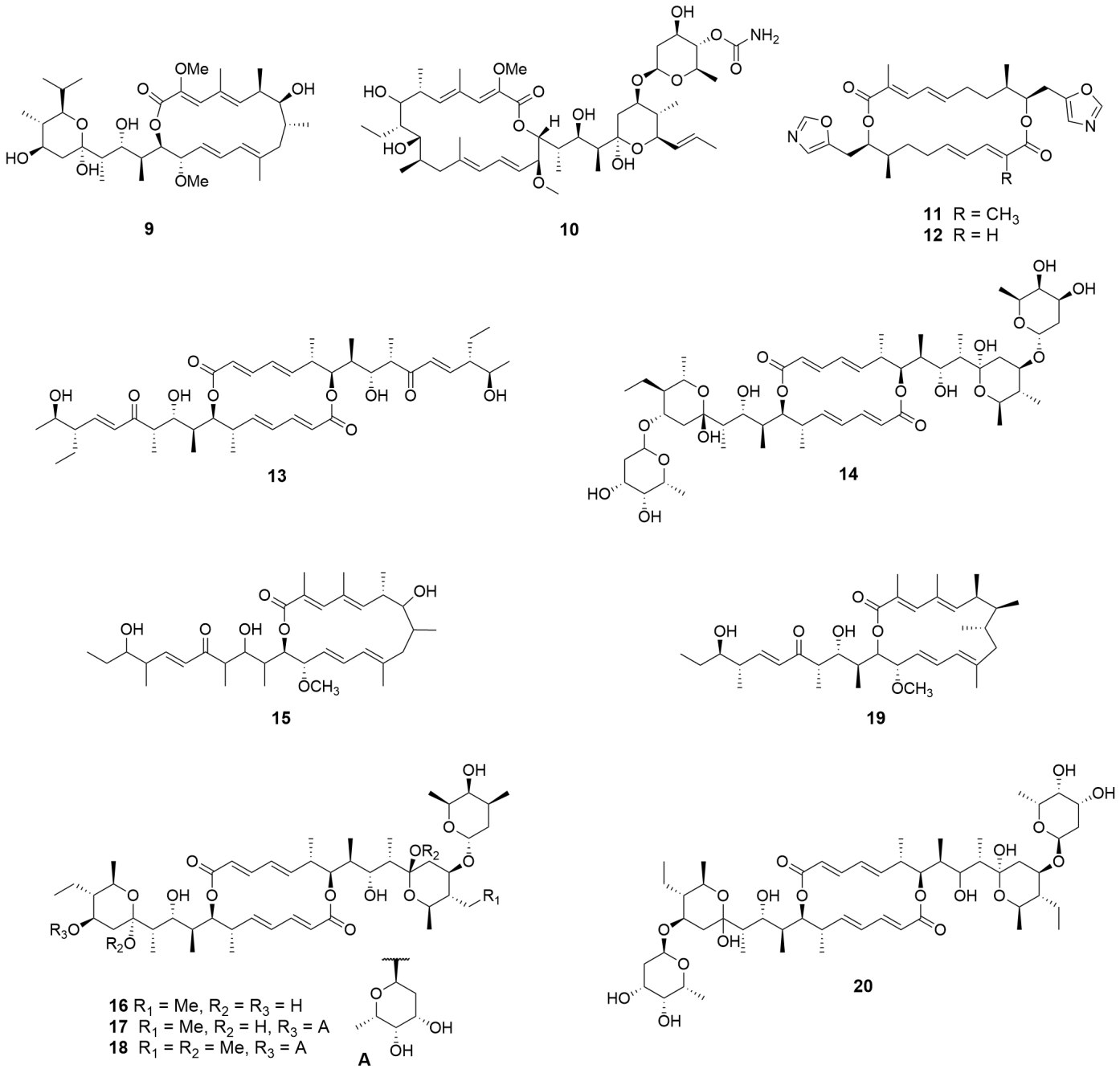


Figure 2. Antiplasmodial macrolides from *Streptomyces*.

from *Streptomyces* NRRL30562 demonstrated strong antiplasmodial activity against *P. falciparum* CSC-1 (Honduras) with very low IC_{50} values of 175 ng/ml, 130 ng/ml, 6.5 ng/ml and 4.5 ng/ml, respectively. More interestingly, the potency of munumbicin D was determined as almost 50% above that of the standard chloroquine and it did not show any observable lysis of human red blood cells up to a concentration of 80 μg/ml which qualified munumbicin D as a good candidate for the development of new malarial drugs (Castillo et al., 2002). Moreover, the same authors characterized two other munumbicins (E-4 and E-5) from *Streptomyces* NRRL3052 which were less potent than the previous ones with IC_{50} values of 0.50 μg/ml and 0.87 μg/ml, respectively, against the same strain of *P. falciparum* CSC-1 (Honduras) (Castillo et al., 2006).

3.2. Polypeptides

Besides the macrolides, another important class of antibiotics from natural sources is represented by the cyclopolypeptides also designated as polyketides. They consist of an association of several amino acids (or peptide) units which can be cyclic or acyclic. Depending on the number of units, we can distinguish

Table 2
Antiplasmodial macrolides from *Streptomyces*.

N°	Name	Strain, IC_{50}	Source	Reference
9	Bafilomycin A1	K1, 0.041 μg/ml	*S. spectabilis* BCC 4785	Isaka et al. (2002)
10	Concanamycin A	K1, 0.2 nM	*Streptomyces* sp.	Auparakkitanon and Wilairat (2006)
11	Samroiyotmycin A	K1, 3.65 μg/ml	*Streptomyces* sp. BCC33756	Dramae et al. (2013)
12	Samroiyotmycin B	K1, 3.16 μg/ml		
13	Efomycin M	K1, 5.23 μg/ml	*Streptomyces* sp. BCC72023	Supong, Thawai, et al. (2016)
14	Efomycin G	K1, 2.37 μg/ml	*Streptomyces* sp. BCC72023	Supong, Sripreechasak, et al. (2016); Supong, Thawai, et al. (2016)
			Streptomyces sp. BCC71188	
15	oxohygrolidin	K1, 2.30 μg/ml	*Streptomyces* sp. BCC72023	Supong, Thawai, et al. (2016)
16	Monoglycosylelaiolide	K1, 2.46 μg/ml		
17	Elaiophylin (or azalomycin)	K1, 0.22 μg/ml	*Streptomyces* sp. BCC71188	Supong, Sripreechasak, et al. (2016)
18	11,11′-Odimethylelaiophylin	K1, 1.47 μg/ml		
19	Oxohygrolidin	K1, 2.30 μg/ml		
20	Elaiophylin	3D7, 777.9 nM	*Streptomyces* sp. USC-16018	Buedenbender et al. (2018)
		Dd2, 598.5 nM		

different subclasses of polypeptides. For instance, the literature survey indicated that six natural occurring antiplasmodial polypeptides including two hexadepsipeptides (**21** and **22**), two heptadepsipeptides (**23** and **24**) and two octadepsipeptides (**42** and **43**) have been reported from *Streptomyces* strains (Table 3 , Figure 3). Furthermore, seventeen new synthetic analogues (**25**– **41**) with significant potencies have been prepared from desoxycyclomarin C (**24**).

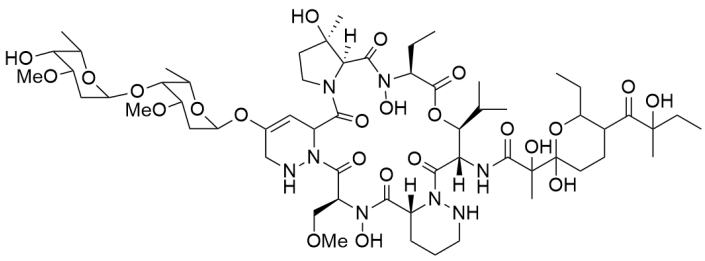
Among the antiplasmodial hexadepsipeptides reported so far from *Streptomyces*, mollemycin A (**21**) is the first glyco-hexadepsipeptide-polyketide isolated from *Streptomyces* sp. CMBM0244 and demonstrating an exceptional potency against the drug-sensitive *P. falciparum* 3D7 and the multidrug-resistant *P. falciparum* Dd2 with IC_{50} values of 7 nM and 9 nM, respectively (Raju et al., 2014), whereas the recent works of Watson et al. (2021) supported that valinomycin (**22**) obtained from *Streptomyces* sp. PR3 displayed potent activity (IC_{50} of 3.75 ng/ml) in a single test against *P. falciparum* NF54, while more interestingly, they found that the activity was increasing in a mixed test when valinomycin was mixed in different ratios with cyclic polypropylene glycols (cPPG). A series of tests revealed that when the cPPG fraction showed an activity of 1792 ng/ml, but the mixtures **22**+cPPG in the fixed ratio 4:1, 3:2, 2:3 and 1:4 will display an increased potency of 1.86 ng/ml, 0.90 ng/ml, 0.75 ng/ml and 0.53 ng/ml, respectively. Their study supported that cPPG can significantly and synergistically improve *in vitro* the antiplasmodial potency of valinomycin (**22**) (Watson et al., 2021).

Cyclomarin C (**23**) and desoxycyclomarin C (**24**) are two natural heptadepsipeptides obtained from *Streptomyces* sp. BCC26924 and *Streptomyces* sp. CNB-982, respectively. Both compounds showed strong antiplasmodial activity indicated by the IC_{50} value of 0.24 μg/ml for cyclomarin C (**23**) against *P. falciparum* K1 and 39.8 nM for desoxycyclomarin C (**24**) against *P. falciparum* 3D7 (Intaraudom et al., 2011; Kiefer et al., 2019). Seventeen new analogues (**25**– **41**) of desoxycyclomarin C have been synthesised and tested against the strains 3D7 and Dd2 of *P. falciparum*. In this regard, the potencies (IC_{50} values) were ranging from 4.4 nM to 452.0 nM against *P. falciparum* 3D7 and from 6.5 nM to 421.5 nM against *P. falciparum* Dd2 (Table 3). The molecular docking performed by the authors suggested that the presence of the *N*'-methyltryptophan unit and the γ,δ-unsaturated side chain might play an important role in the improvement of the antiplasmodial potencies of the synthesised analogues (Kiefer et al., 2019).

Finally, two octadepsipeptides viz octaminomycins A (**42**) and B (**43**) were previously obtained from *Streptomyces* sp. RK85-270 and tested for their antiplasmodial activity against three *P. falciparum* strains including the drug-sensitive strain 3D7 and the two multidrug-resistant strains Dd2 and K1. The results showed that both compounds possessed the same activity against *P. falciparum* 3D7 with IC_{50} of 1.5 μM, while compound **42** was more active than **43** against the two other strains with IC_{50} values of 1.6 μM and 1.3 μM for compound **42** against *P. falciparum* Dd2 and K1, respectively; while compound **43** displayed IC_{50} values of 1.1 μM and 0.85 μM, respectively. Additionally, the two compounds were more pharmacologically interesting due to their no significant cytotoxicity against human cervical cancer cells (HeLa), human promyelocytic leukaemia cells (HL-60), mouse temperature-sensitive cdc2 mutant cells (tsFT210), and rat kidney cells that were infected with ts25 (srcts-NRK) at the highest concentration of 30 μM (Jang et al., 2017).

3.3. Anthraquinones

Four C-glycosylated benz[α]anthraquinones urdamycinones E (**44**) and G (**45**), dehydroxyaquayamycin (**46**) as well as urdamycin E (**47**) were isolated from the marine *Streptomyces* sp. BCC45596 and displayed potent antiplasmodial activity against P. falciparum K1 with IC_{50} values of 0.0534 μg/ml, 0.142 μg/ml, 2.93 μg/ml and 0.173 μg/ml, respectively (Supong et al., 2012). The comparison of the potency with their structural changes (Table 4 , Figure 4) suggested that the free angular hydroxy groups in their structures might play an important



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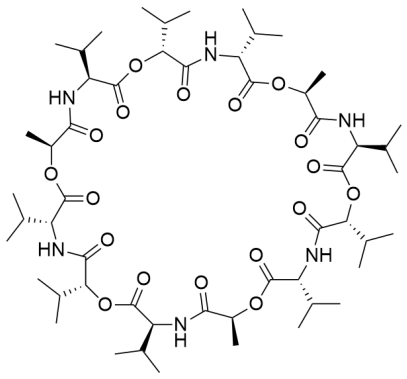

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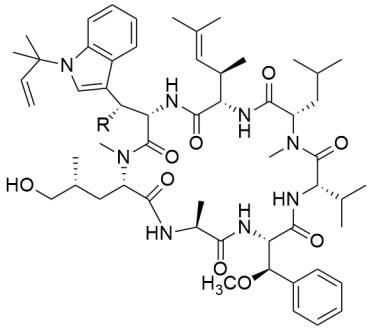
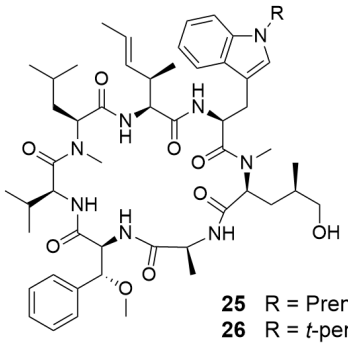
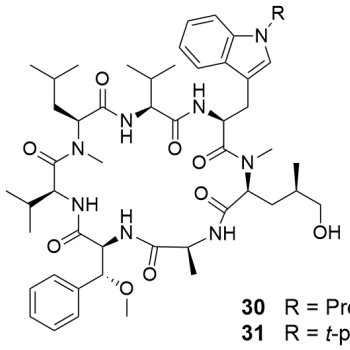


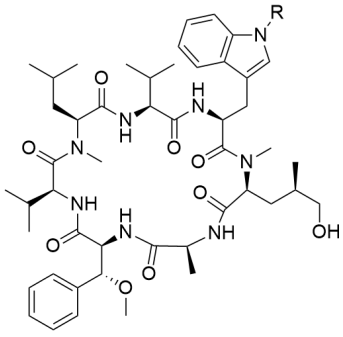
23 R = OH
24 R = H

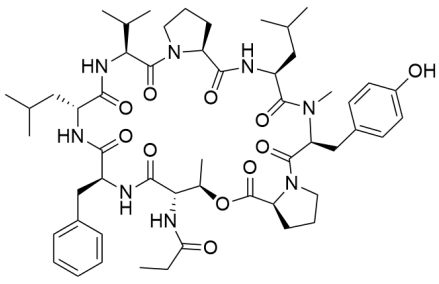


25 R = Prenyl
26 R = *t*-pentyl
27 R = *i*-Pr
28 R = Me
29 R = H

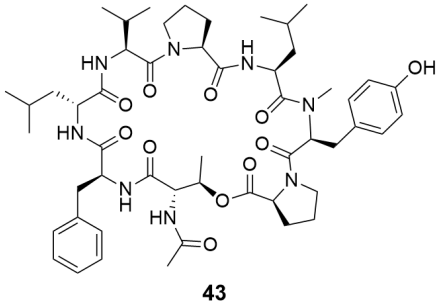


30 R = Prenyl
31 R = *t*-pentyl
32 R = *i*-Pr
33 R = Me
34 R = H





42



43

35 R_1 = Prenyl, R_2 = (1*R*,*E*)-1-methylbut-2-enyl
36 R_1 = *t*-pentyl, R_2 = (1*R*,*E*)-1-methylbut-2-enyl
37 R_1 = *i*-Pr, R_2 = (1*R*,*E*)-1-methylbut-2-enyl
38 R_1 = Me, R_2 = (1*R*,*E*)-1-methylbut-2-enyl
39 R_1 = Prenyl, R_2 = i-propyl
40 R_1 = *t*-pentyl, R_2 = i-propyl
41 R_1 = H, R_2 = i-propyl

Figure 3. Antiplasmodial polypeptides from *Streptomyces*.

Table 3
Antiplasmodial polypeptides from *Streptomyces*.

N°	Name	Strain, IC_{50}	Source	Reference
21	Mollemycin A	3D7, 7 nM Dd2, 9 nM	*Streptomyces* sp. (CMBM0244)	Raju et al. (2014)
22	Valinomycin	NF54, 3.75 ng/ml	*Streptomyces* sp. PR3	Watson et al. (2021)
23	Cyclomarin C	K1, 0.24 μg/ml	*Streptomyces* sp. BCC26924	Intaraudom et al. (2011)
24	Desoxycyclomarin C	3D7, 39.8 nM	*Streptomyces* sp. CNB-982	
25	Compound 25a	3D7, 9.0 nM Dd2, 12.9 nM	Synthetic analogue	
26	Compound 25b	3D7, 4.4 nM Dd2, 6.5 nM	Synthetic analogue	
27	Compound 25c	3D7, 47.8 nM Dd2, 76.0 nM	Synthetic analogue	
28	Compound 25d	3D7, 13.4 nM Dd2, 17.8 nM	Synthetic analogue	
29	Compound 25e	3D7, 28.1 nM Dd2, 27.5 nM	Synthetic analogue	
30	Compound 28a	3D7, 34.4 nM Dd2, 71.8 nM	Synthetic analogue	
31	Compound 28b	3D7, 57.6 nM Dd2, 200.2 nM	Synthetic analogue	
32	Compound 28c	3D7, 355.7 nM Dd2, 300.3 nM	Synthetic analogue	Kiefer et al. (2019)
33	Compound 28d	3D7, 230.3 nM Dd2, 256.7 nM	Synthetic analogue	
34	Compound 28e	3D7, 314.2 nM Dd2, 421.5 nM	Synthetic analogue	
35	Compound 34a	3D7, 47.9 nM Dd2, 36.7 nM	Synthetic analogue	
36	Compound 34b	3D7, 452.0 nM Dd2, 346.5 nM	Synthetic analogue	
37	Compound 34c	3D7, 177.5 nM Dd2, 287.8 nM	Synthetic analogue	
38	Compound 34d	3D7, 362.4 nM Dd2, 318.4 nM	Synthetic analogue	
39	Compound 35a	3D7, 303.5 nM Dd2, 260.8 nM	Synthetic analogue	
40	Compound 35b	3D7, 428.5 nM Dd2, 305.1 nM	Synthetic analogue	
41	Compound 35e	3D7, 287.4 nM Dd2, 196.7 nM	Synthetic analogue	
42	Octaminomycin A	3D7, 1.5 μM Dd2, 1.6 μM K1, 1.3 μM	*Streptomyces* sp. RK85-270	Jang et al. (2017)
43	Octaminomycin B	3D7, 1.5 μM Dd2, 1.1 μM K1, 0.85 μM		

role in the activity. Furthermore, the increasing of sugar units slightly reduced the potency of the tested compounds. In addition to that four C-glycosylated benz[α]anthraquinones, four other anthraquinones have been obtained from the culture of the terrestrial *Streptomyces* sp. BCC27095 and identified as steffimycins B (**48**) and C (**49**), 10-dihydrosteffimycin B (**50**) and 7-deoxysteffimycinone (**51**). However, compound **49** showed strong activity against *P. falciparum* K1 with IC_{50} of 0.53 μM, while compounds **48**, **50** and **51** demonstrated a good activity with IC_{50} values of 4.76 μM, 2.19 μM and 8.03 μM, respectively (Intaraudom et al., 2015).

3.4. Geldanamycin analogues

Another important class of antiplasmodial compounds from *Streptomyces* is composed of geldanamycin (**52**) and its congeners 17-odemethylgeldanamycin (**53**), 17-demethoxyreblastatin (**54**) isolated from the terrestrial *Streptomyces* sp. BCC71188, as well as herbimycin G (**55**) obtained from the marine *Streptomyces* sp. USC-16018 (Supong et al. 2016b;) (Buedenbender et al., 2018). Geldanamycin (**52**) and 17-demethoxyreblastatin (**54**) gave similar strong potencies of IC_{50} values 0.35 μg/ml and 0.31 μg/ml, respectively, against *P. falciparum* K1, while 17-odemethylgeldanamycin (**54**) was moderately active with an IC_{50} value of 1.90 μg/ml against the same parasitic strain (Table 5). More recently, the research works carried out by Buedenbender et al. (2018) dealt with the identification of herbimycin G (**55**) containing a geldanamycin scaffold in its structure. Compound **55** showed at 40 μM, 77.2% inhibition of *P. falciparum* 3D7 and 81.7% inhibition of *P. falciparum* Dd2 (Buedenbender et al., 2018). The structures of the antiplasmodial geldanamycin derivatives are presented in Figure 5 .

3.5. Pactamycin analogues

Pactamycin (**56**) is a well-known antibiotic discovered by the Upjohn Company in the early 1960s and has been reported during the last decades from *Streptomyces pactum* ATCC 27456 by Almabruk et al. (2013). During their investigations, the authors also isolated two other pactamycin analogues indexed TM-025 (**57**) and TM-026 (**58**) (Figure 6) which were submitted to mutasynthetic strategy to generate their fluorinated derivatives TM-025F (**59**) and TM-026F (**60**), respectively. All five compounds were screened for their antiplasmodial activity against three *P. falciparum* strains including the chloroquine-sensitive strain D6 and two multidrug-resistant strains Dd2 and 7G8. The results (Table 6) showed that pactamycin (**56**) was the most active compound against the three strains, while its congeners compounds **57** and **58**, as well as their fluorinated derivatives **59** and **60**, were slightly less active against the three strains with IC_{50} values ranging from 3.9 nM to 39.1 nM which remains in an excellent range of activity for all the compounds (Almabruk et al., 2013).

3.6. Polyether compounds

From the literature accessed during our survey, three compounds described as polyethers have been isolated from *Streptomyces* sp. and described as demonstrating an antiplasmodial activity (Table 7, Figure 7). Abierixin (**61**) and its methylated derivative 29-*O*-methylabierixin (**62**) were isolated from *Streptomyces* sp. BCC72023 showed a moderate potency against *P. falciparum* K1 with IC_{50} values of 2.58 μg/ml and 1.40 μg/ml, respectively, while compound **63** isolated from *Streptomyces* sp. H668 was active against *P. falciparum* D6 and W2 with IC_{50} ranging from 100 to 200 ng/ml (Na et al., 2008; Supong, Thawai, et al., 2016).

3.7. Diketopiperazines

Two diketopiperazines (**64** and **65**) and one dimeric diketopiperazine (**66**) have been reported as antiplasmodial agents from *Streptomyces* strains (Table 8, Figure 8). Thus, the chemical investigations of the isolate S1 of *Streptomyces* sp. led to the isolation of piperafizine A (**64**) demonstrating activity of IC_{50} equal to 6.57 μM against *P. falciparum* Dd2 (Rakotondraibe et al., 2015), whereas another diketopiperazine identified as L-Pro-L-Leu (**65**) was obtained from *Streptomyces* sp. USC-16018 with 45.9 % inhibition of *P. falciparum* 3D7 and 39.0 % inhibition of *P. falciparum* Dd2 at 40 μM (Buedenbender et al., 2018). A dimeric analogue called naseseazine C (**66**) was reported in 2016 from the culture of *Streptomyces* sp. and was moderately active against *P. falciparum* 3D7 with an IC_{50} of 3.52 μM (Buedenbender et al., 2016).

3.8. Miscelleaneous

Several other specialised metabolites from *Streptomyces* have been identified as antiplasmodial principles (Table 9, Figure 9). Among them, farneside A (**67**) was reported as a sesquiterpenoid nucleoside ether from *Streptomyces* sp. CNT-372 with moderate activity (IC_{50} of 69.3 μM) against *P. falciparum* 3D7 while 2-methylthio-N^7-methyl-cis-zeatin (**68**), the first N^7-methylated zeatin-type natural product has been reported from *Streptomyces* sp. 80H647 with a GI_{50} of 2.4 μM against the same parasite (Ilan et al., 2013; Lopez et al., 2000). One polyenoic acid amide natural product named annimycin B (**69**) and a metabolite containing a γ-butyrolactone and 2-hydroxy-3-formylaminobenzoic acid moieties called opantimycin A (**70**) showed weak activity with 30% inhibition of *P. falciparum* Dd2, HB3, 3D7 at 2.5 μM; and IC_{50} of 13 μg/ml against *P. falciparum* 3D7, respectively (Zhang et al. 2014;) (Nogawa et al., 2017).

One benzoisochromanequinone frenolicin B (**71**) obtained from *Streptomyces roseofulvus* displayed good antiplasmodial activity against *P. falciparum* HB3, Dd2 and 7G8 with IC_{50} values of 600 nM, 800 nM and 800 nM, respectively (Fitzgerald et al., 2011). Similarly, the carbazole antibiotics named carbazomycins B (**72**) and C (**73**) were obtained from *Streptomyces* sp. BCC27095, as well as the tripyrrole pigment metacycloprodigiosin (**74**) and the nitrophenyl-substituted polyketide spectinabilin (**75**) from *Streptomyces spectabilis*

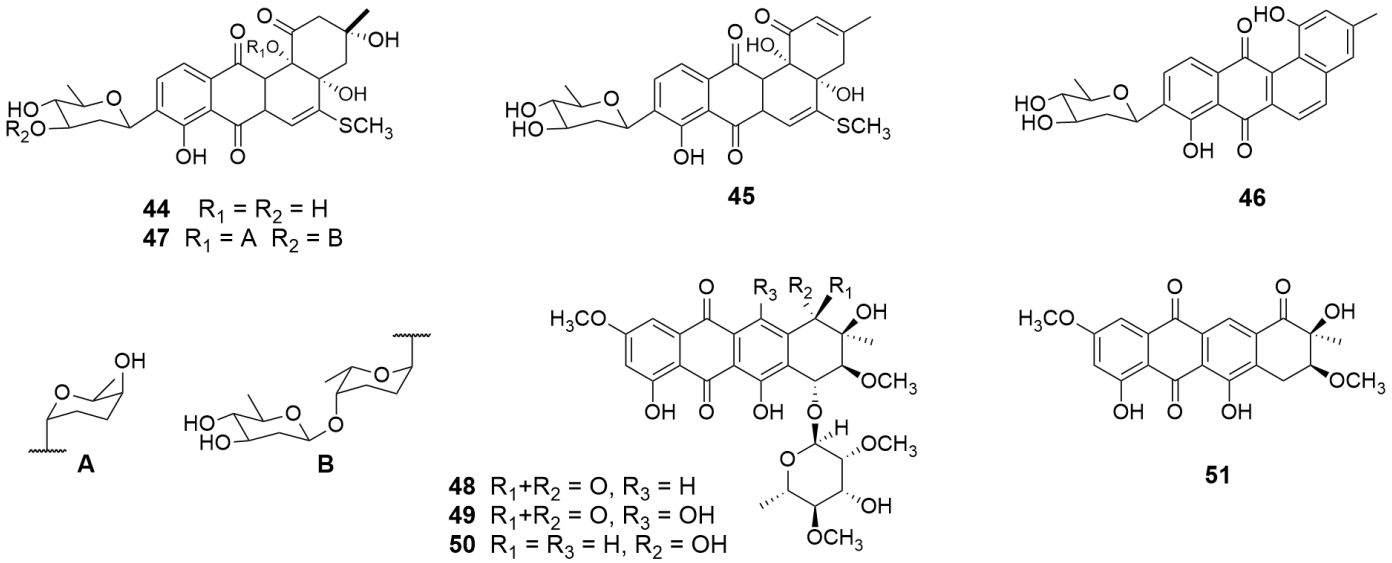


Figure 4. Antiplasmodial anthraquinones from Streptomyces

Table 4
Antiplasmodial anthraquinones from *Streptomyces*.

N°	Name	Strain, IC 50	Source	Reference
44	Urdamycinone E	K1, 0.0534 μg/ml		
45	Urdamycinone G	K1, 0.142 μg/ml	*Streptomyces* sp. BCC45596	Supong et al. (2012)
46	dehydroxyaquayamycin	K1, 2.93 μg/ml		
47	urdamycin E	K1, 0.173 μg/ml		
48	steffimycin B	K1, 2.19 μM		
49	Steffimycin C	K1, 0.53 μM	*Streptomyces* sp. BCC27095	Intaraudom et al. (2015)
50	10-Dihydrosteffimycin B	K1, 4.76 μM		
51	7-deoxysteffimycinone	K1, 8.03 μM		

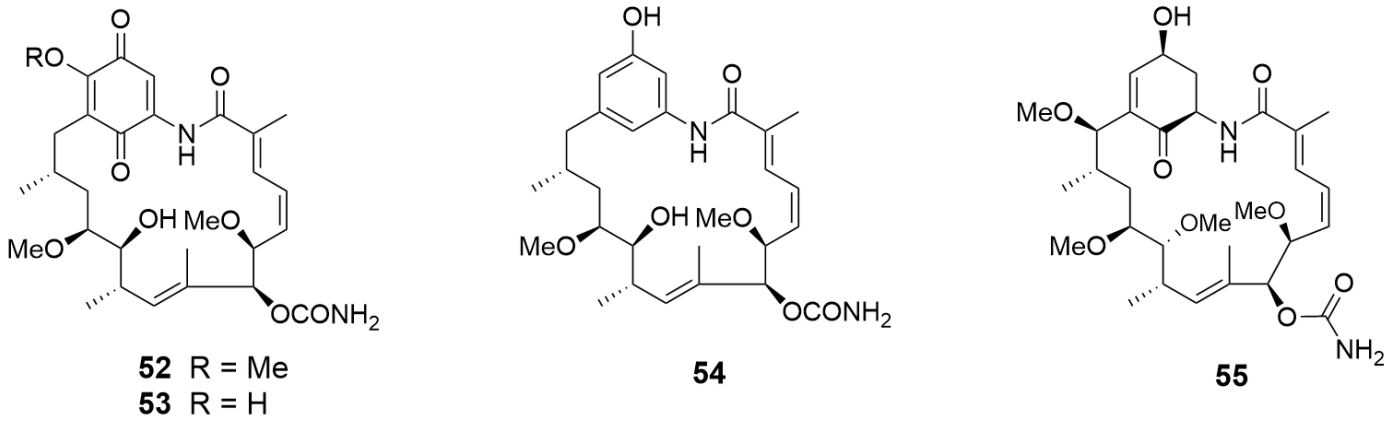


Figure 5. Antiplasmodial geldanamycin analogues from *Streptomyces*.

Table 5
Antiplasmodial geldanamycin analogues from *Streptomyces*.

N°	Name	Strain, IC 50	Source	
52	Geldanamycin	K1, 0.35 μg/ml		
53	17-Odemethylgeldanamycin	K1, 1.90 μg/ml	*Streptomyces* sp. BCC71188	Supong, Sripreechasak, et al. (2016)
54	17-demethoxyreblastatin	K1, 0.31 μg/ml		
55	Herbimycin G	3D7, 77.2 % Inhib. at 40 μM	*Streptomyces* sp. USC-16018	Buedenbender et al. (2018)
		Dd2, 81.7 % Inhib. at 40 μM		

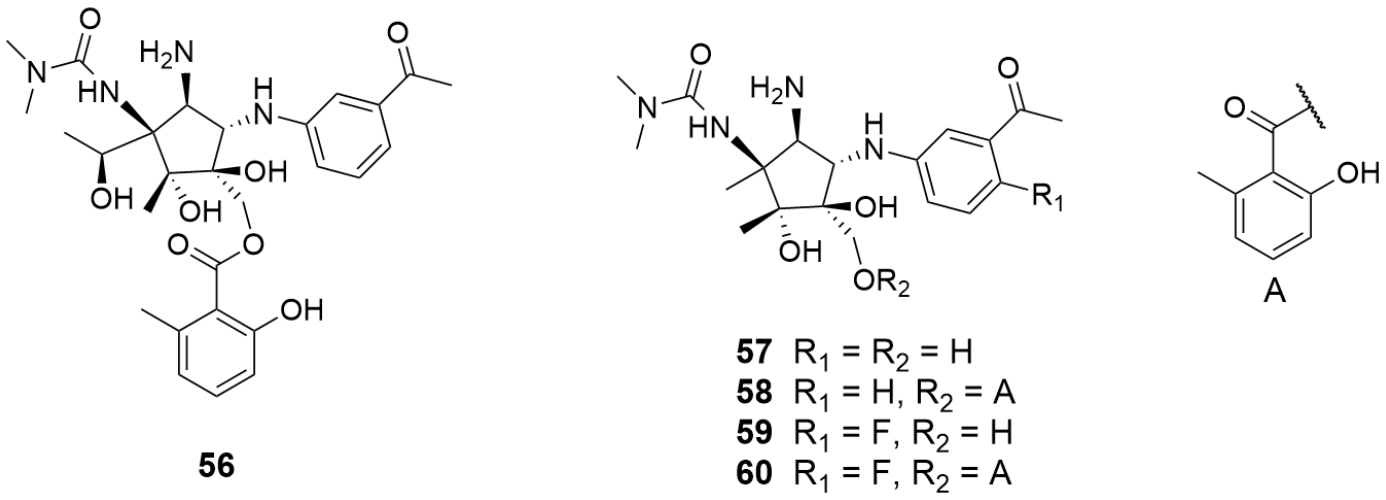


Figure 6. Antiplasmodial pactamycin analogues from *Streptomyces*.

Table 6
Antiplasmodial pactamycin analogues from *Streptomyces*.

N°	Name	Strain, IC $_{50}$	Source	Reference
56	Pactamycin	D6, 4.9 nM Dd2, 3.9 nM 7G8, 4.2 nM	*Streptomyces pactum* ATCC 27456	
57	TM-025	D6, 7.7 nM Dd2, 10.5 nM 7G8, 7.1 nM	*Streptomyces pactum* ATCC 27456	
58	TM-026	D6, 11.5 nM Dd2, 14.0 nM 7G8, 9.1 nM	*Streptomyces pactum* ATCC 27456	Almabruk et al. (2013)
59	TM-025F	D6, 12.3 nM Dd2, 16.8 nM 7G8, 12.4 nM	Synthetic	
60	TM-026F	D6, 26.5 nM Dd2, 39.1 nM 7G8, 24.9 nM	Synthetic	

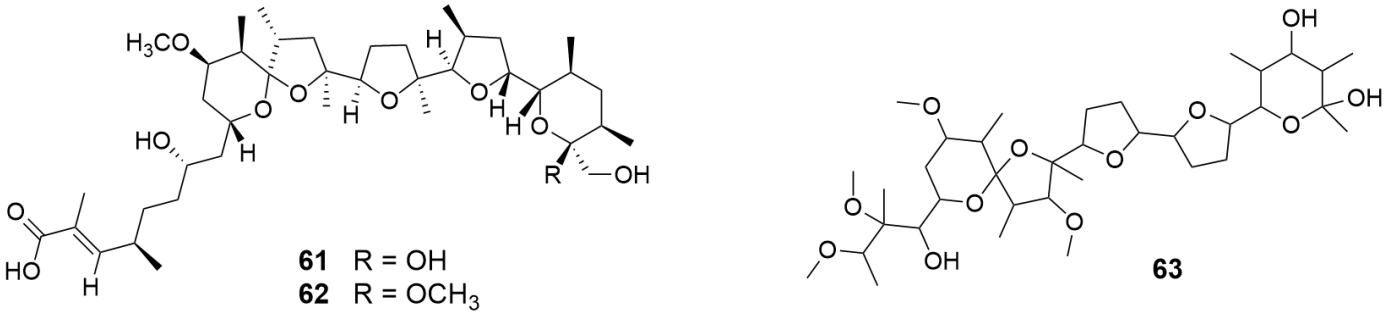


Figure 7. Antiplasmodial polyethers from *Streptomyces.*

Table 7
Antiplasmodial polyethers from *Streptomyces.*

N°	Name	Strain, IC $_{50}$	Source	Reference
61	abierixin	K1, 2.58 μg/ml	*Streptomyces* sp. BCC72023	Supong, Thawai, et al. (2016)
62	29-O-methylabierixin	K1, 1.40 μg/ml		
63	//	D6 and W2, 100 – 200 ng/ml	*Streptomyces* sp. H668	Na et al. (2008)

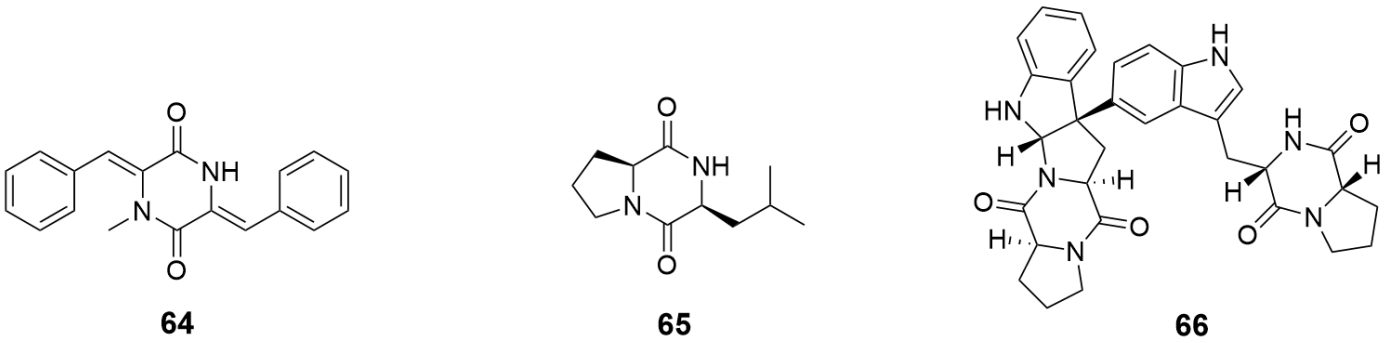


Figure 8. Antiplasmodial diketopiperazines from *Streptomyces*.

Table 8
Antiplasmodial diketopiperazines from *Streptomyces*.

N°	Name	Strain, IC_{50}	Source	Reference
64	Piperafizine A	Dd2, 6.57 μM	*Streptomyces* isolate S.1	Rakotondraibe et al. (2015)
65	L-Pro-L-Leu	3D7, 45.9 % Inhib. at 40 μM	*Streptomyces* sp. USC-16018	Buedenbender et al. (2018)
		Dd2, 39.0 % Inhib. at 40 μM		
6	Naseseazine C	3D7, 3.52 μM	*Streptomyces* sp.	Buedenbender et al. (2016)

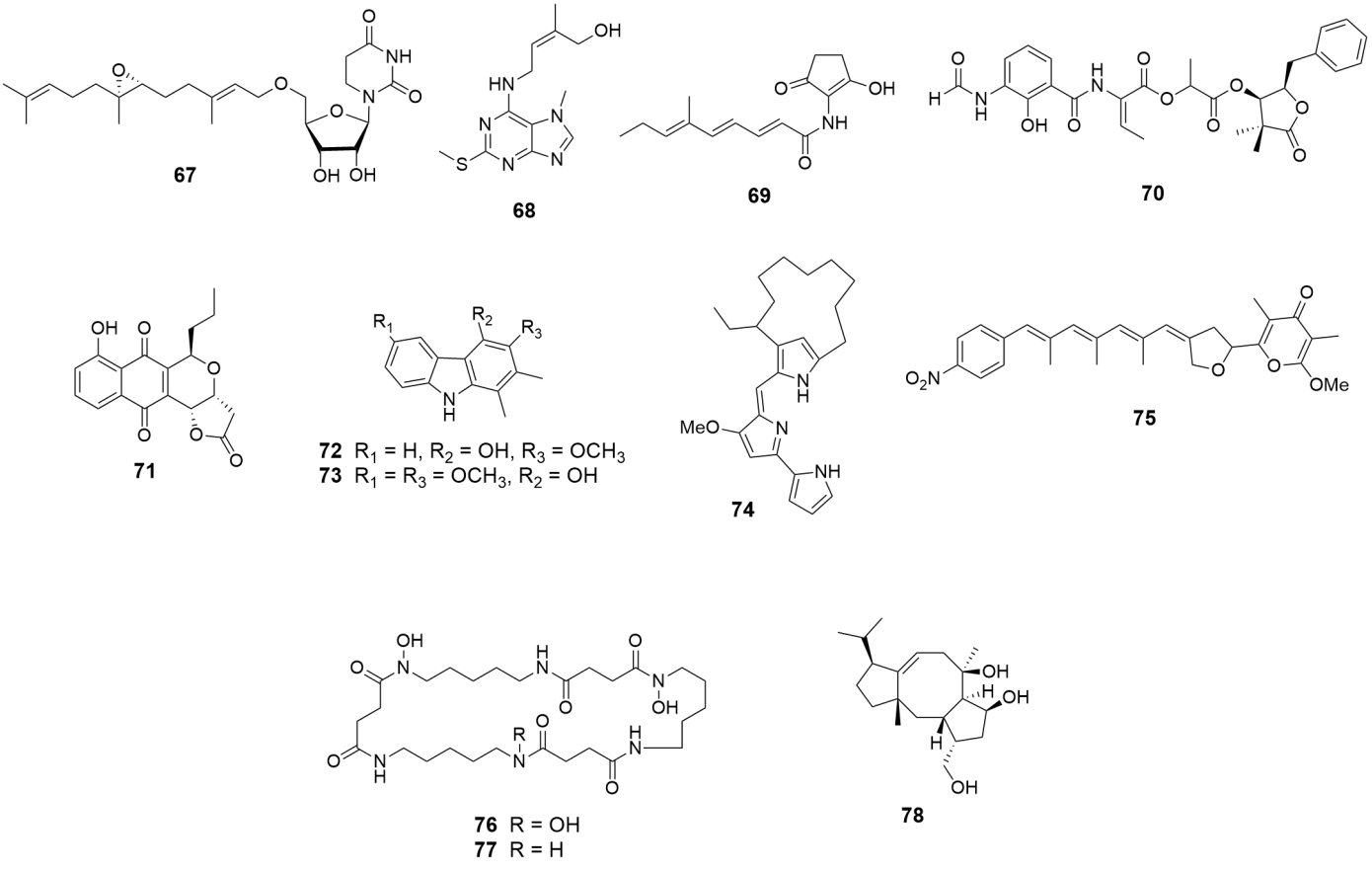


Figure 9. Other antiplasmodial compounds from *Streptomyces*.

Table 9
Other antiplasmodial compounds from *Streptomyces*.

N°	Name	Strain, IC $_{50}$	Source	Reference
67	Farneside A	3D7, 69.3 μM	*Streptomyces* sp. CNT-372	Ilan et al. (2013)
68	2-Methylthio-N^7-methyl-cis-zeatin	3D7, GI50 2.4 μM	*Streptomyces* sp. 80H647	Lopez et al. (2000)
69	Annimycin B	Dd2, HB3 and 3D7, 30% of inhib. at 2.5 μM	*S. asterosporus* DSM 41452	Zhang et al. (2018)
70	Opantimycin A	3D7, 13 μg/ml	*Streptomyces* sp. RK88-1355	Nogawa et al. (2017)
71	Frenolicin B	HB3, 600 nM Dd2, 800 nM 7G8, 800 nM	*Streptomyces roseofulvus*	Fitzgerald et al. (2011)
72	Carbazomycin B	K1, 2.37 μg/ml	*Streptomyces* sp. BCC26924	Intaraudom et al. (2011)
73	Carbazomycin C	K1, 2.10 μg/ml		
74	Metacycloprodigiosin	K1, 0.0050 μg/ml	*S. spectabilis* BCC 4785	Isaka et al. (2002)
75	Spectinabilin	K1, 7.8 μg/ml		
76	Nocardamine	K1, 3.20 μg/ml	*Streptomyces* sp.BCC71188	Supong, Sripreechasak, et al. (2016)
77	Dehydroxynocardamine	K1, 2.63 μg/ml		
78	Cyclooctatin	K1, 7.14 μg/ml		

BCC4785, were all evaluated against *P. falciparum* K1 and only compound **74** gave a strong activity with IC_{50} of 0.0050 μg/ml while compounds **72** and **73** gave a moderate activity with IC_{50} values of 2.37 μg/ml and 2.10 μg/ml, respectively; and finally, compound **75** was the less active with an IC_{50} of 7.8 μg/ml (Intaraudom et al., 2011; Isaka et al., 2002).

Two cyclopeptides namely nocardamine (**76**) and its derivative dehydroxynocardamine (**77**) have been isolated and characterized from *Streptomyces* sp. BCC71188. Both compounds were tested against P. falciparum K1 and found to be moderately active with IC_{50} values of 3.20 μg/ml and 2.63 μg/ml, respectively (Supong, Sripreechasak, et al., 2016). Finally, the diterpenoid cyclooctatin (**78**) was obtained from the chemical investigations of *Streptomyces* sp. BCC71188 gave a moderate activity with an IC_{50} of 7.14 μg/ml against *P. falciparum* K1 (Supong, Sripreechasak, et al., 2016).

4. CONCLUSION AND FUTURE PROSPECTS

The data provided by the literature on the antiplasmodial compounds from *Streptomyces* support that these bacteria represent important sources of bioactive metabolites that can be considered as interesting candidates for new drugs discovery. In addition to be well reported as antibiotics, many *Streptomyces*-derived compounds demonstrated strong activities and were in some cases more effective than the reference drugs. For instance, three compounds including the macrolide munumbucin D and the two octadepsipeptides octaminomycins A (**42**) and B (**43**) displayed good antiplasmodial activity and did not show any cytotoxicity against several cell lines that increases their pharmacological interest for new drug development. Additional close checking indicated that several other compounds from *Streptomyces* have displayed strong or good potency against the drug-resistant strain K1 of *P. falciparum*. Among them, bafilomycin A1 (**9**), concanamycin A (**10**), elaiophylin (**17**), cyclomarin C (**23**), urdamycinone E (**44**), geldanamycin (**52**) and metacycloprodigiosin (**74**) demonstrated strong antiplasmodial with IC_{50} values of 0.041 μg/ml, 0.2 nM, 0.22 μg/ml, 0.24 μg/ml, 0.0534 μg/ml, 0.35 μg/ml and 0.0050 μg/ml, respectively, against *P. falciparum* K1. Inded, the discovery of a new compound with high potency against a chloroquine-resistant strain of *P. falciparum* like K1 or Dd2 might be a good starting point to address the problem of resistance of *P. falciparum* to prescribed drugs which is one of the most important factors to control in the eradication of malaria. Overall, despite the interesting *in vitro* antiplasmodial activity recorded so far for the indicated compounds, further *in vivo*, pharmacokinetic or ADMET studies are necessary to obtain more insights on their action mechanism, solubility or toxicity which are important to manufacturing a drug.

CONFLICTS OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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J.D.W : Conceptualization, Funding acquisition, Formal analysis, Methodology, Supervision, Project administration, Resources, Validation, Writing – review & editing

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