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Review

Antimalarials from nature

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ABSTRACT

Malaria is a major public health problem mainly due to the development of resistance by the most lethal causative parasitic species, *Plasmodium falciparum* to the mainstay drugs like chloroquine. New drugs with unique structures and mechanism of action are urgently required to treat sensitive and drug-resistant strains of malaria. Historically, compounds containing novel structure from natural origin represent a major source for the discovery and development of new drugs for several diseases. This review presents recent advances in antimalarial drug discovery from natural sources, including plant extracts, and compounds isolated from plants, bacteria, fungi and marine organisms. These compounds offer new and novel scaffolds for development as antimalarials. The literature from 1998 to October 2008 is reviewed. The review present literature compilation from plant and marine extracts, alkaloids (naphthylisoquinolines, bisbenzylisoquinolines, protoberberines and aporphines, indoles, manzamines, and miscellaneous alkaloids) terpenes (sesquiterpenes, triterpenes, diterpenes, and miscellaneous terpenes) quassinoids, flavonoids, limonoids, chalcones, peptides, xanthones, quinones and coumarines, and miscellaneous antimalarials from nature. The review also provides an outlook to recent semisynthetic approaches to antimalarial drugs discovered from natural sources.

Contents

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1. Introduction

Malaria kills 1–2 million people each year and 300–500 million new clinical cases of malaria are reported annually.[1] Malaria is a particularly devastating disease in sub-Saharan Africa, where about 90% of cases and deaths occur. Malaria is also a serious public health problem in certain regions of South East Asia and South America. Human malaria transmitted by female *Anopheles* mosquitoes is caused by four species of *Plasmodium*, which are, *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Most cases of malaria and deaths are caused by *P. falciparum*. The development of resistance to mainstay drugs like chloroquine, and controlled use of new artemisinin analogs have created an urgent need to discover new antimalarial agents.

The life cycle, immunological defense mechanisms, and clinical development of malaria in humans is a complex process.[2] Clinical malaria is characterized by periodic fever, which follows the lysis of infected erythrocytes, and caused mainly by the induction of cytokines interleukin-1 and tumor necrosis factor. *P. falciparum* infection can have serious effects, for example, anemia, cerebral complications (from coma to convulsions), hypoglycemia and glomerulonephritis. The disease is most serious in the non-immune individuals, including children, pregnant women and tourists.

Nature remains an ever evolving source for compounds of medicinal importance. The use of medicinal plants for the treatment of parasitic diseases is well known and documented since ancient times. For example, use of *Cinchona succiruba* (Rubiaceae) for the treatment of malaria infection is known for centuries. Several compounds isolated from nature also form a rich source of diverse structures for optimization to obtain improved therapeutics. A number of natural products having antimalarial activities have been reviewed.[3–8] This review focuses on the status of antimalarials discovered during last 10 years from all natural sources, including crude plant extracts, marine based bioactive natural products, isolated and identified promising compounds from plants, bacteria, and fungi. Attempts have been made to provide an exhaustive compilation on structural features of antimalarials isolated from natural sources and to provide insights into their properties, including advantages and limitations in malaria chemotherapy. The review covers antimalarials from plant and marine extracts, alkaloids, terpenes, quassinoids, flavonoids, limonoids, chalcones, peptides, xanthones, quinones and coumarines, and miscellaneous antimalarials from nature. This review also discusses recent advances in approaches to semisynthetic antimalarials.

2. Plant and marine extracts

Baelmans et al. screened 178 plant extracts from the Pharmacopeia of the Bolivian ethnia Tacana. Five extracts from *Aloysia virgata*, *Bixa orellana*, *Caesalpinia pluviosa*, *Mascagnia stannea* and *Trichilia pleenea* demonstrated more than 70% inhibition of hematin polymerization at 2.5 mg/mL.[9] Of the 18 medicinal plants from Sierra Leone examined by Marshall et al. *Triclisia patens* showed significant antiplasmodial activity (IC_{50} = 8.0 μg/mL).[10] *Cissampelos pareira*, *Cordia polycephala*, *Trichilia hirta*, *Turnera ulmifolia* and *Lippia alba* from the flora of Puerto Rico showed 50–100% parasite suppression at 5 μg/mL.[11] The acetone fraction of the stem bark of the Ethiopian medicinal plant *Combretum molle* showed significant activity against trophozoites of *P. falciparum* (IC_{50} = 8.17 μg/mL). The antimalarial effect was attributed to the presence hydrolysable tannins, punicalagin (**1**) Figure 1 (IC_{50} = 27.73 μg/mL), and CM-A (IC_{50} = 11.66 μg/mL).[12] The root extracts of the Tanzanian medicinal plant *Abutilon grandiflorum* showed prominent in vivo activity against *P. vinckei* in mice and in vitro against *P. falciparum* strains HB3 and FCB, with moderate cytotoxicity to the colon cell line HT29.[13] *Bidens pilosa* a medicinal plant has antimalarial activity, which is attributed to flavonoid and acetylene compounds.[14] Andrade-Neto et al. showed that chloroquine-resistant or mefloquine-resistant *P. falciparum* strains display in vitro susceptibility to *B. pilosa* (IC_{50} = 10.4–49.8 μg/mL). Interestingly, extracts from plants cultivated under standardized conditions were less active compared to wild plants.[15] Rasoanaivo et al. screened 190 plants from five different ecosystems of Madagascar to search naturally occurring antimalarial compounds.[16] Thirty nine plants displayed in vitro activity against *P. falciparum* (IC_{50} < 5.0 μg/mL), while nine had IC_{50} ranged in 5–7.5 μg/mL. Tasdemir et al. evaluated Turkish plants for antiplasmodial activities and inhibition of plasmodial enoyl-ACP reductse (FabI), a crucial enzyme involved in the fatty acid biosynthesis.[17] The most potent extracts were from *Phlomis kurdica*, *P. leucophracta*, *Scrophularia cryptophila*, *Morina persica* and *Asperula nitida* (IC_{50} ranging from 1.5 to 1.9 μg/mL). The extracts of leaves of *Rhododendron ungernii* (IC_{50} = 10 μg/mL) and *R. smirnovii* (IC_{50} = 0.4 μg/mL) strongly inhibited the FabI enzyme. The preliminary data indicated that some (poly)phenolic compounds were responsible for the FabI inhibition potential of these extracts. The essential oil obtained from leaves of *Cymbopogon citratus* and *Ocimum gratissimum* showed significant antimalarial activity in vivo (62.1–86.6% and 55.0–77.8% suppression of parasitemia, respectively) at concentrations of 200, 300 and 500 mg/kg in *P. berghei* infected mice model.[18] The main constituents of the oil of *Ocimum gratissimum* were γ-terpinene, β-phellandrene, limonene, thymol and that of *C. citratus* geranial, neral, myrcene and β-pinene. Okokon et al. studied the antimalarial activity of ethanolic stem-bark extract of *Cylicodiscus gabunensis* in vivo in mice infected with *P. berghei* during early and established infections as well as for repository activity.[19] The LD_{50} of the extract was determined to be 223.6 mg/kg, while doses ⩾250 mg/kg were lethal to mice. Of the 204 extracts tested from Brazilian Cerrado plants, 32 (15.7%) showed significant parasite growth inhibition at 10.0 μg/mL.[20] The most active species showed IC_{50} values ranging from 0.9 μg/mL (Flacourtiaceae and Sapindaceae) to 4.9 μg/mL (Apocynaceae and Annonaceae). Out of forty-nine plants screened from South Vietnam, significant antiplasmodial activities (IC_{50} = 0.4–8.6 μg/mL) have been reported with good selectivity from six plants: *Arcangelisia flava* and *Fibraurea tinctoria*, *Harrisonia perforata*, *Irvingia malayana*, *Elaeocarpus kontumensis* and *Anneslea fragrans*.[21] Muthaura et al. found three plant species, *Maytenus putterlickioides*, *Warburgia stuhlmannii* and *Pentas bussei* from the Kwale community, to possess antimalarial activities in low micromolar concentrations.[22] Garavito et al. reported that eight vegetal extracts from Columbia displayed good antiplasmodial activity (IC_{50} <1–2.1 μg/mL), while in the in vivo model only *Abuta grandifolia* alkaloidal crude extract exhibited activity, inhibiting 66% of the parasite growth at 250 mg/kg/day.[23] In combination with CQ, extracts of Kenyan medicinal plants: *Toddalia asiatica*, *Rhamnus prinoides*, *Vernonia lasiopus*, *Maytenus acuminata*, *M. heterophylla* and *Rhamnus staddo* showed improved parasitemia suppression from 38% to 66% and resulted into longer survival of mice, indicating synergistic interactions.[24] This was attributed to the immunomodulatory role of the plant extracts on the immune system of the host during early days of infection. Muthaura et al. evaluated plant extracts of Meru for in vitro and in vivo antiplasmodial, cytotoxic-

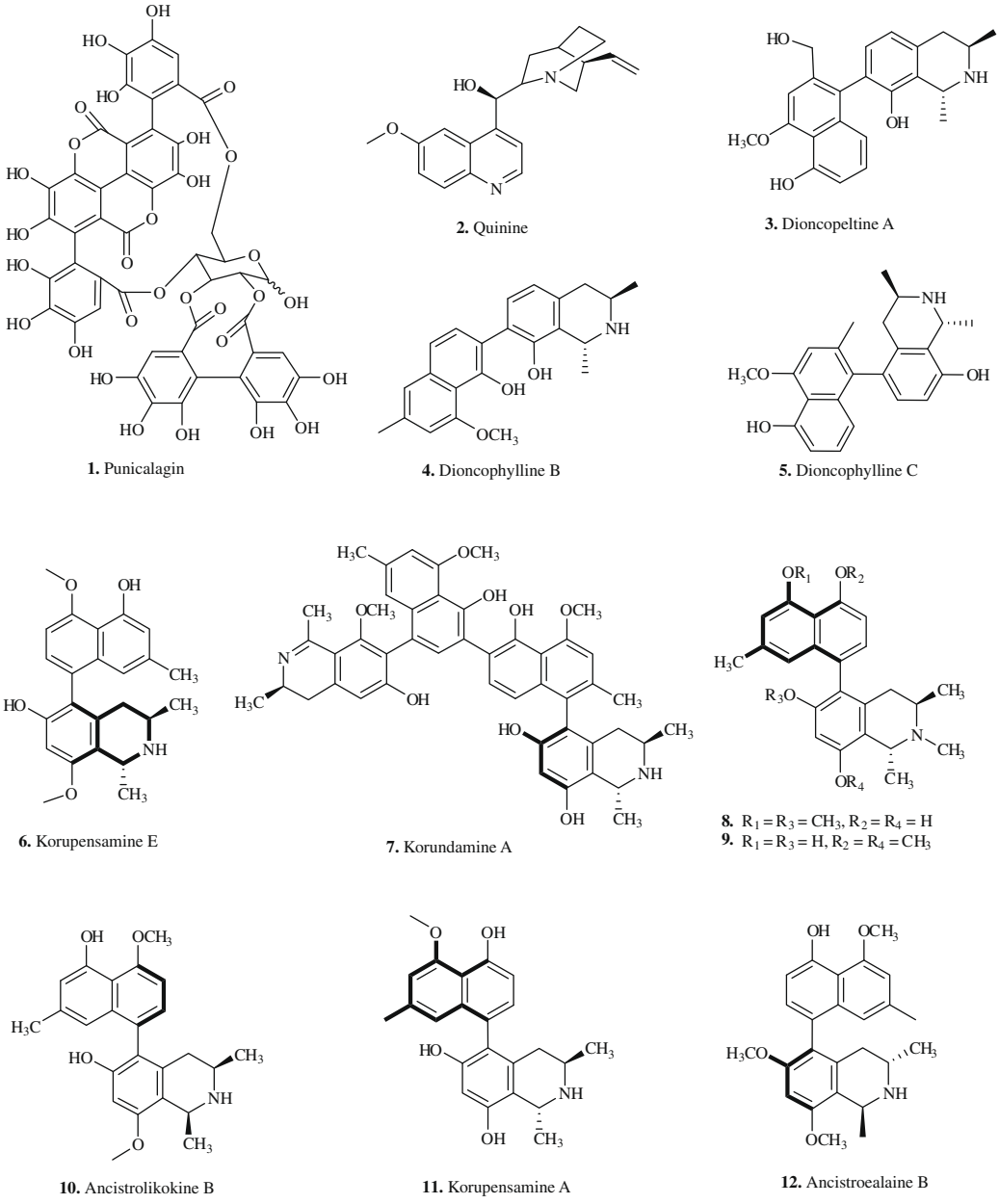


Figure 1. Antimalarial alkaloids.

ity and animal toxicity activities. The extracts of *Ludwigia erecta*, *Fuerstia africana* and *Schkuhria pinnata* exhibited antiplasmodial activity (IC_{50} <5 μg/mL), with high selectivity index of 124.[25] Of a total of 27 aqueous extracts collected from different marine species, on the northwest Cuban coast, three species of tunicates: *Microcosmus goanus*, *Ascidia sydneiensis* and *Phallusia nigra* inhibited parasite growth by 50% at concentrations of 17.5, 20.9 and 29.4 μg/mL, respectively.[26]

3. Alkaloids

Alkaloids are one of the most important classes of natural products providing drugs since ancient times. Alkaloids are the physiologically-active nitrogenous bases derived from biogenetic precursors. A number of alkaloids are well known because of their toxicity or use as psychodelic drugs (e.g., cocaine, morphine or the semisynthetic LSD). At the same time, alkaloids have been successfully used for the treatment of parasitic infections. The outstanding example is quinine (**2**, Fig. 1) from *Cinchona succirubra* (Rubiaceae) used for the treatment of malaria for more than three centuries. Alkaloids based antimalarials discussed herein are divided into naphthylisoquinolines, bisbenzylisoquinolines, protoberberines and aporphines, indoles, manzamines, and miscellaneous alkaloids.

3.1. Naphthylisoquinoline alkaloids (Figs. 1 and 2)

Dioncopeltine A (**3**), dioncophylline B (**4**) and dioncophylline C (**5**) isolated from the extracts of *Triphyophyllum peltatum* (Dioncophyllaceae), exhibited high antiplasmodial activity in *P. berghei* infected mice.[27] Dioncophylline C (**5**) cured infected mice completely after oral treatment with 50 mg kg^{-1} day^{-1} for 4 days without noticeable toxic effects. Korupensamine E (**6**), a monomeric alkaloid (IC_{50} = 2.0 μg/mL)[28] and korundamine A (**7**) a heterodi-

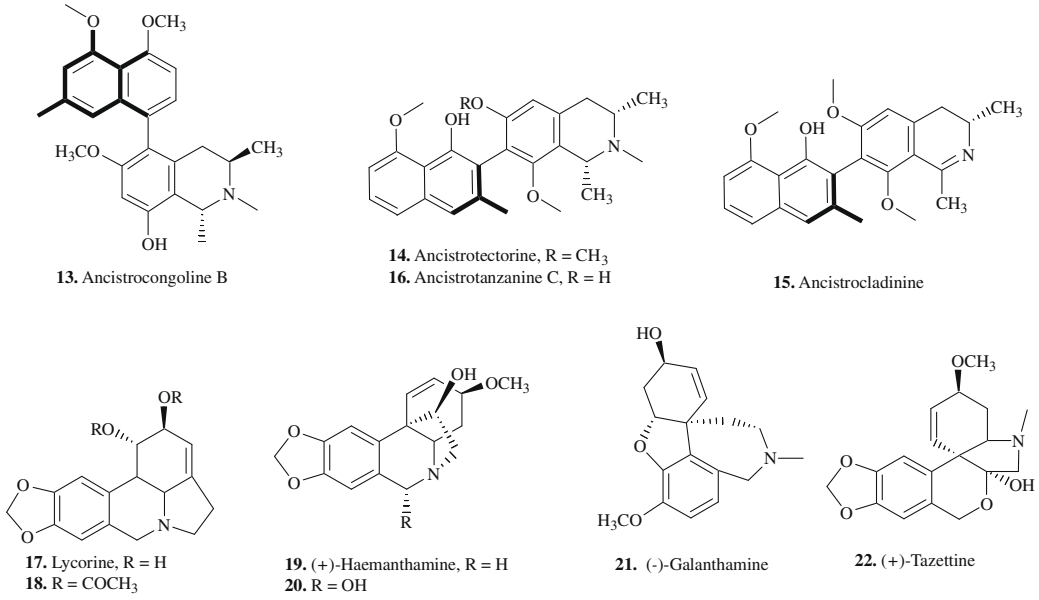


Figure 2. Antimalarial alkaloids.

meric alkaloid (IC_{50} = 1.1 μg/mL)[29] against *P. falciparum* were obtained from *Ancistrocladus korupensis* (Ancistrocladaceae, biogenetically related to Dioncophyllaceae). Structure–activity relationship indicated that presence of a secondary amine function and absence of an oxygen substituent at C-6, and (*R*)-configuration at C-3 are important. Ancistrolikokines A, C and B (**8**–**10**), and Korupensamine A (**11**) isolated from *Ancistrocladus likoko* showed good to moderate antimalarial activities in vitro with IC_{50} values of 191, 6232, 538 and 24 ng/mL and 140, 924, 208 and 72 ng/mL against *P. falciparum* NF54 strain and K1 strain, respectively.[30] The lower activities of less polar **8**–**10** were in agreement with the observation that the presence of free hydroxy groups is essential for potent antimalarial activity of naphthylisoquinoline alkaloids.

5,8′-Coupled naphthylisoquinoline alkaloid, ancistroealaine-B (**12**) from *Ancistrocladus ealaensis* exhibited activity against *P. falciparum* (IC_{50} = 0.52 μg/mL). Ancistroealaine-B (**12**) represented pure 'ancistrocladaceae-type' alkaloid, *S*-configured at C-3 and equipped with an oxygen function at C-6.[31] Bringmann et al. reported ancistrocongolines A–D from *Ancistrocladus congolensis* along with the known alkaloid Korupensamine A.[32] All compounds exhibited antiplasmodial activities with ancistrocongoline-B (**13**) being the most active (IC_{50} = 0.15 μg/mL). All ancistrocongolines and Korupensamine A are representatives of 'hybrid-type' naphthoisoquinolines, with 3*R*-configuration and oxygen functionality at C-6, bearing both structural features of 'ancistrocladaceae-type' alkaloids and the 'dioncophyllaceae-type' alkaloids (3*R*, no oxygen at C-6). 7,3′-Coupled ancistrotectorine (**14**), ancistrocladidine (**15**) and ancistrotanzanine C (**16**), possessing antimalarial activities against the K1 strain (IC_{50} = 0.1–0.7 μg/mL) have been reported from *Ancistrocladus tanzaniensis*.[33] William et al. isolated four alkaloids, lycorine (**17**), 1,2-di-*O*-acetyllycorine (**18**), ambelline and crinine, from the bulbs of *Brunsvigia littoralis* (Amaryllidaceae).[34] Alkaloids **17** and **18** displayed best activity (IC_{50} = 0.62 and 1.0 μg/mL, respectively), but were cytotoxic.

Orhan et al. isolated four groups of alkaloids, lycorine, crinine, tazettine, and galanthamine exhibiting antimalarial activity at different potencies, from amaryllidaceae plants namely *Pancratium maritimum*, *Leucojum aestivum*, and *Narcissus tazetta*, found in Turkey.[35] Haemanthamine (**19**), and 6-hydroxyhaemanthamine (**20**) were active with IC_{50} of 0.70 and 0.34 μg/mL respectively, against *P. falciparum* (T9.96), while galanthamine (**21**, IC_{50} = 4.38 μg/mL) and tazettine (**22**, IC_{50} = 5.42 μg/mL) had least activity against *P. falciparum* (K1). Difference in the chemical structures of these alkaloids could be responsible for variation in their antimalarial activities. Except galanthamine and tazettine, the other alkaloids have no N-methylated side chain. Lycorine and crinine alkaloids contain methylenedioxy-side chain attached to the benzene ring of the molecule, suggesting that the methylenedioxybenzene part of the molecule and tertiary nitrogen without methyl group contribute to higher activity of both lycorine and crinine groups of alkaloids than galanthamine and tazettine group of alkaloids.

3.2. Bisbenzylisoquinoline alkaloids (Fig. 3)

In bisbenzylisoquinolines, the two moieties are usually bound by one or more diaryl ether bridges, although carbon–carbon bridges or a methylene-oxy bridge may also be present. The bisbenzylisoquinoline alkaloids can be divided into three categories: biscoclaurines, coclaurin-reticulines and bisreticulines, according to the nature, the number, and the attachment point of the bridges. In each subgroup, the alkaloids differ by the nature of their oxygenated substituents, the degree of the unsaturation in the heterocyclic rings, and the stereochemistry of their two chiral centers, C-1 and C-1′.

Angerhofer et al. tested 53 bisbenzylisoquinoline alkaloids for antiplasmodial activity and cytotoxicity against mammalian cells.[36] The alkaloids in general exhibited antiplasmodial activity (IC_{50} ranged in 29–1500 nM against D6 clone, and IC_{50} ranged in 59–4030 nM against W2 clone of *P. falciparum*). The most selective alkaloids were (−)-cycleanine (**23**), (+)-cycleatjehine (**24**), (+)-cycleatjehenine (**25**), (+)-malekulatine (**26**), (−)-repandine (**27**), and (+)-temuconine (**28**). Among these, **26** is a bisreticuline derivative, while all other are biscoclaurines. (+)-Malekulatine (**26**) is a head-to-tail dimer, while (+)-temuconine (**28**) is linked tail-to-tail. In (−)-repandine (**27**) the two bisbenzylisoquinoline moieties are linked by two etheroxy bridges between C-7,C-8′ and C-11,C-12′. (−)-Cycleanine (**23**) had two etheroxy bridges at C-8,C-12′ and C-12,C-8′. In (+)-cycleatjehine (**24**) and (+)-cycleatjehenine (**25**) possessing a pyridine ring, the bisbenzoisoquinoline moieties were linked by an etheroxy bridge at C-11,C-7′ and by a methylenoxy bridge at C-7,C-12′. Demethylation at C-12 decreased the selectivity as in case of **24**. Mambu et al. have reported strong antiplasmodial activity of (−)-curine (**29**) and isochondodendrine (**30**) isolated from the stem bark of *Isolona ghesquiereina* (IC_{50} = 353 and 892 nM,

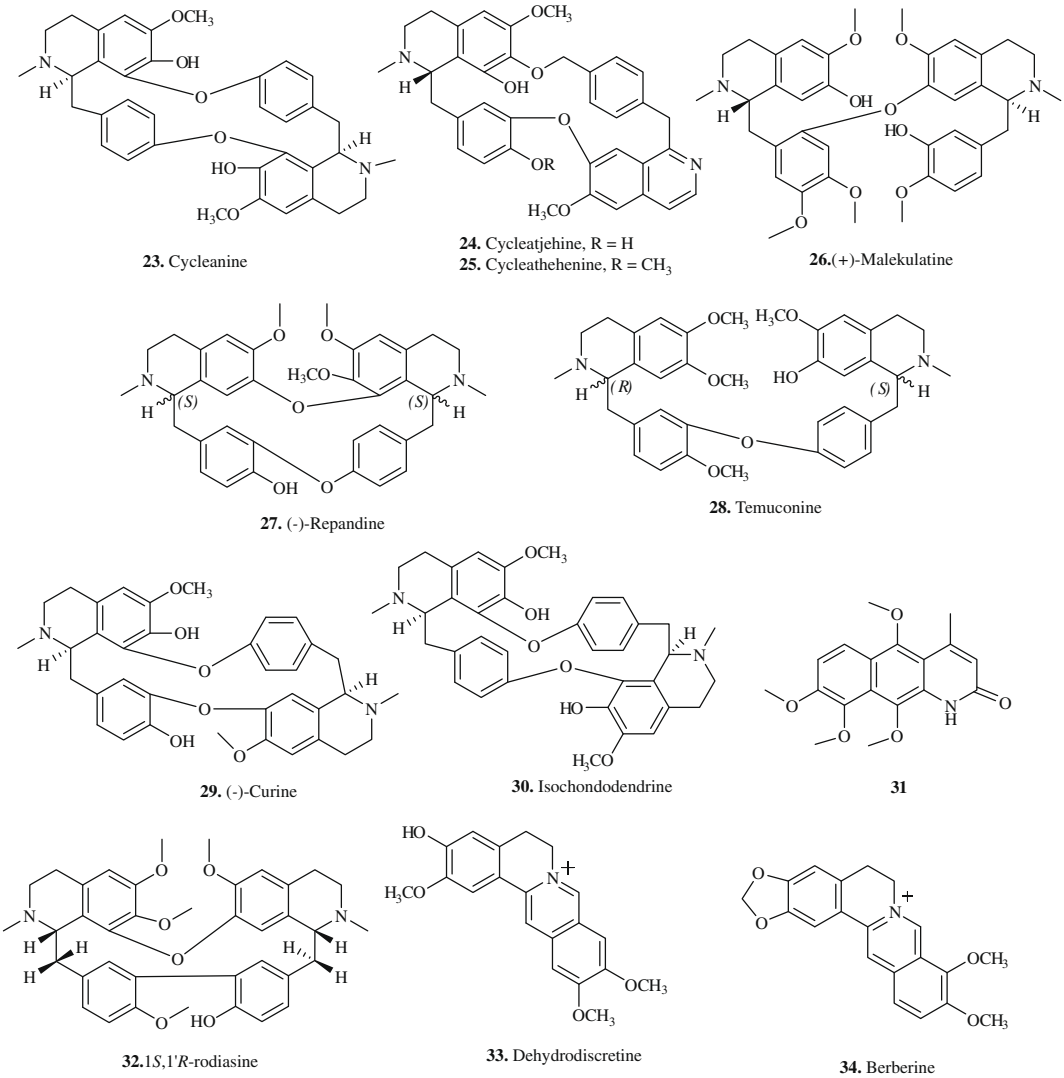


Figure 3. Antimalarial alkaloids.

respectively).[37] *Pseudoxandra cuspidata* bark has good antimalarial activity and recently its bio-assay-guided fractionation by Roumy et al. led to the isolation of an unusual azaanthracene alkaloid **31** (IC_{50} = 42.92 μM), a bis-benzylisoquinoline alkaloid (1*S*, 1'*R*)-rodiasine (**32**, IC_{50} = 1.14 μM) along with alkaloids *O*-methyl-punjabine and *O*-methyl-moschatoline.[38] The antimalarial activity of this bark was mostly due to **32**, which was most active and least toxic of these alkaloids.

3.3. Protoberberine and aporphine alkaloids (Figs. 3 and 4)

Wright et al. evaluated antimalarial activities of several protoberberine group containing alkaloids, which exhibited promising antiplasmodial activities.[39] Dehydrodiscretine (**33**, IC_{50} = 0.64 μM) and berberine (**34**, IC_{50} = 0.96 μM) were the most active. Canadine (**35**) a tetrahydroberberine, was less active indicating that presence of quaternary nitrogen is required for the activity of protoberberines. The two alkaloids also had different saturation in ring C as a consequence of the quaternization of the ring-B nitrogen. In the aporphine group, norcorydine (**36**) possessed the highest antiplasmodial activity (IC_{50} = 3.08 μM), and corydine, its *N*-methyl analogue, was sevenfold less active. Isocorydine, which differed from corydine in the positioning of the hydroxyl/methoxyl substituents, and catalpifoline (6-*O*-methylnorcorydine) were also less active than corydine suggesting that a secondary amino function and a phenolic substituent enhance the in vitro antiplasmodial activity of aporphines.[39] Long-Ze et al. reported the cytotoxicity and promising antimalarial activity of phenolic aporphine-benzylisoquinoline alkaloids **37**, **38** and **39** (IC_{50} = 24.2, 10.2 and 11.2 ng/mL, respectively) isolated from the roots of *Thalictrum faberi*.[40] Hadranthine A (**40**) and B (**41**) are 4,5-dioxo-1-azaaporphinoids obtained from *Duguetia hadrantha*.[41] Alkaloid **40** exhibited in vitro antimalarial activity against *P. falciparum* with IC_{50} = 120 ng/mL and selectivity index of >40, while **41** was inactive.

3.4. Indole alkaloids (Figs. 4 and 5)

Mendiol et al. have recently reviewed the antiplasmodial indole alkaloids isolated from natural sources.[42] 10′-Hydroxyusambarensine (**42**), a tertiary phenolic bisindole alkaloid isolated from the roots of *Strychnos usambarensis* displayed modest antimalarial activity (IC_{50} = 0.16 μg/mL, W2 strain).[43] Paulo et al. tested aqueous and ethanolic extracts of *Cryptolepis sanguinolenta* and seven alkaloids isolated from these extracts against K1 and T996 strains of *P. falciparum*.[44] The indolobenzazepine alkaloid cryptoheptine (**43**) was the second most active in this series after cryptolepine (**44**) (IC_{50} = 0.8 and 0.23 μM, respectively). The study showed that

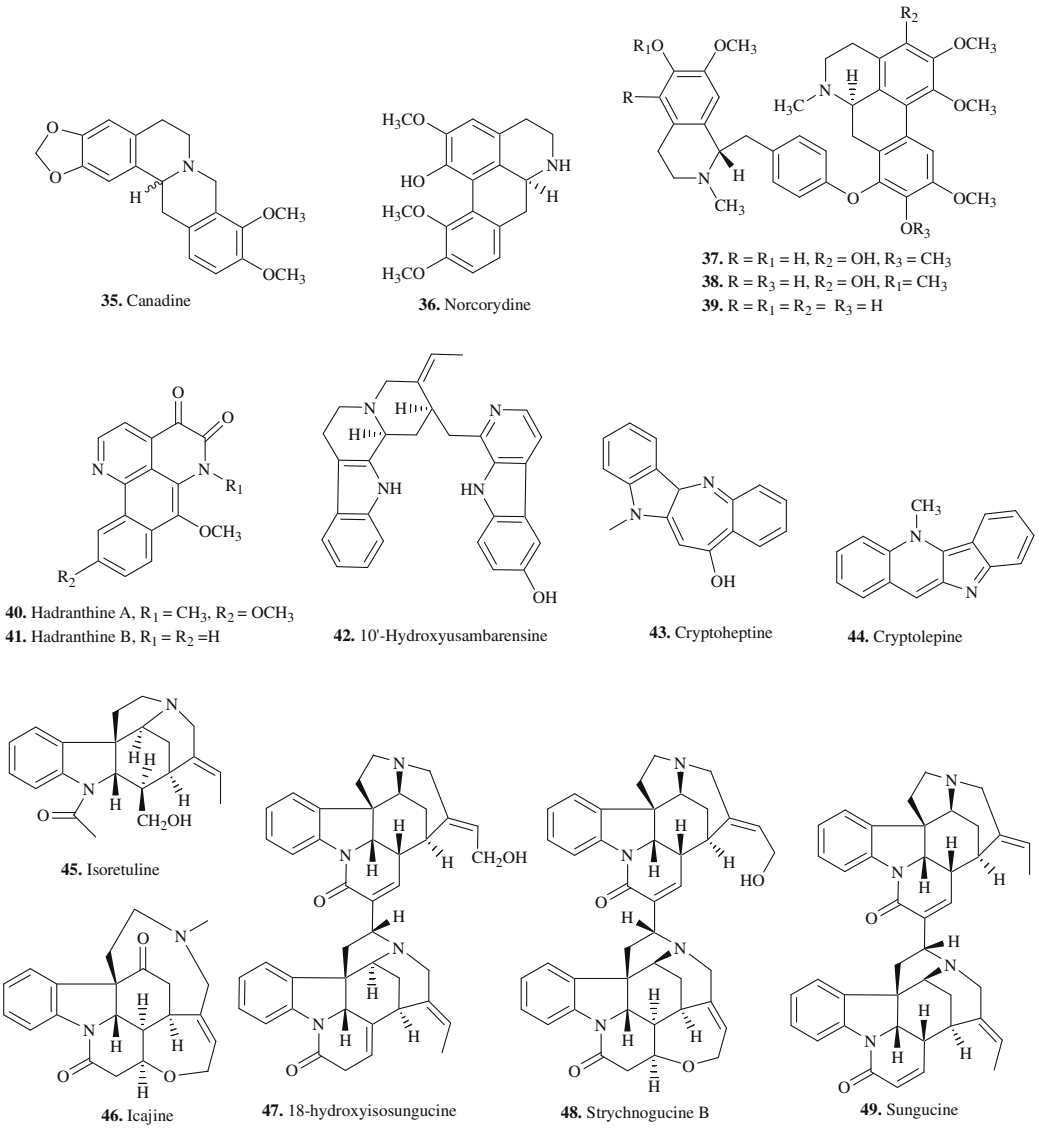


Figure 4. Antimalarial alkaloids.

alkaloids with weakly basic characteristics were active, whereas structurally related alkaloids with different acid–base profiles were inactive, suggesting they have similar mode of action as that of quinolines. Frédérich et al. evaluated eight naturally occurring monoindole alkaloids in vitro for their ability to inhibit *P. falciparum* growth, in drug combination and to reverse resistance of a chloroquine (CQ)-resistant strain.[45] Three alkaloids icajine, isoretuline and strychnobrasiline reversed CQ resistance at concentrations between 2.5 and 25.0 μg/mL, with an interaction factor (IF) of 12.82 for isoretuline (**45**) on W2 strain. Only icajine (**46**) was found synergistic with mefloquine (IF = 15.38). No synergy was observed between CQ and alkaloids on the CQ-sensitive D6 strain. Active alkaloids did not possess any substitution on their indole moiety and had H-16α configuration. A substitution on the indolic moiety suppressed the CQ-potentiating activity.

Many dimeric or trimeric indolomonoterpenic alkaloids with antiplasmodial properties have been isolated from root-bark of *Strychnos icaja*, a liana found in Central Africa.[46–49] Frédérich et al. found that bisindole alkaloids particularly the sungucine alkaloids possessed interesting antimalarial activity. The modification of the double bond from 23′–17′ into 16′–17′ and introduction of a hydroxy substituent at C-18 induced an increase of the antimalarial activity as in 18-hydroxyisosungucine (**47**) (IC_{50} = 0.14 μM, W2 strain). In the in vitro assays against chloroquine-resistant *P. falciparum* strychnogucine B (**48**) a tertiary quasi-symmetric bisindole alkaloid, was more active than sungucine (**49**) (IC_{50} = 0.085 and 10 μM, respectively).

Frédérich et al. have reported alkaloids consisting of four types of bisindole skeleton exhibiting potent and selective activities against *Plasmodium*. They were sungucine-type (IC_{50} values ranged in 80 nM to 10 μM), longicaudatine-type (IC_{50} values ranged in 0.5–10 μM), matopensine-type (IC_{50} values ranged in 150 nM to 10 μM), and usambarine-type (IC_{50} values ranged in 100–150 nM). All active compounds were tertiary dimers and a certain degree of basicity was necessary for the antiplasmodial activity. For example, usambarine (**50**) possessing a methyl substituent at N'_4 was less active than ochrolifuanine A (**51**) having a N'_4–H and isostrychnopentamine (**52**) with a third basic nitrogen in pyrrolidine ring. Also, matopensine-type N-oxide (**53**) or quaternary derivatives were less active than the respective tertiary compounds. Reduced activity may be attributed to the ionic nature of N-oxides. In the case of sungucine-type alkaloids, antiplasmodial selectivity was associated with the presence of a 16′–17′ double bond or a 17′–18′ ether link. The trimeric indolomonoterpene alkaloid

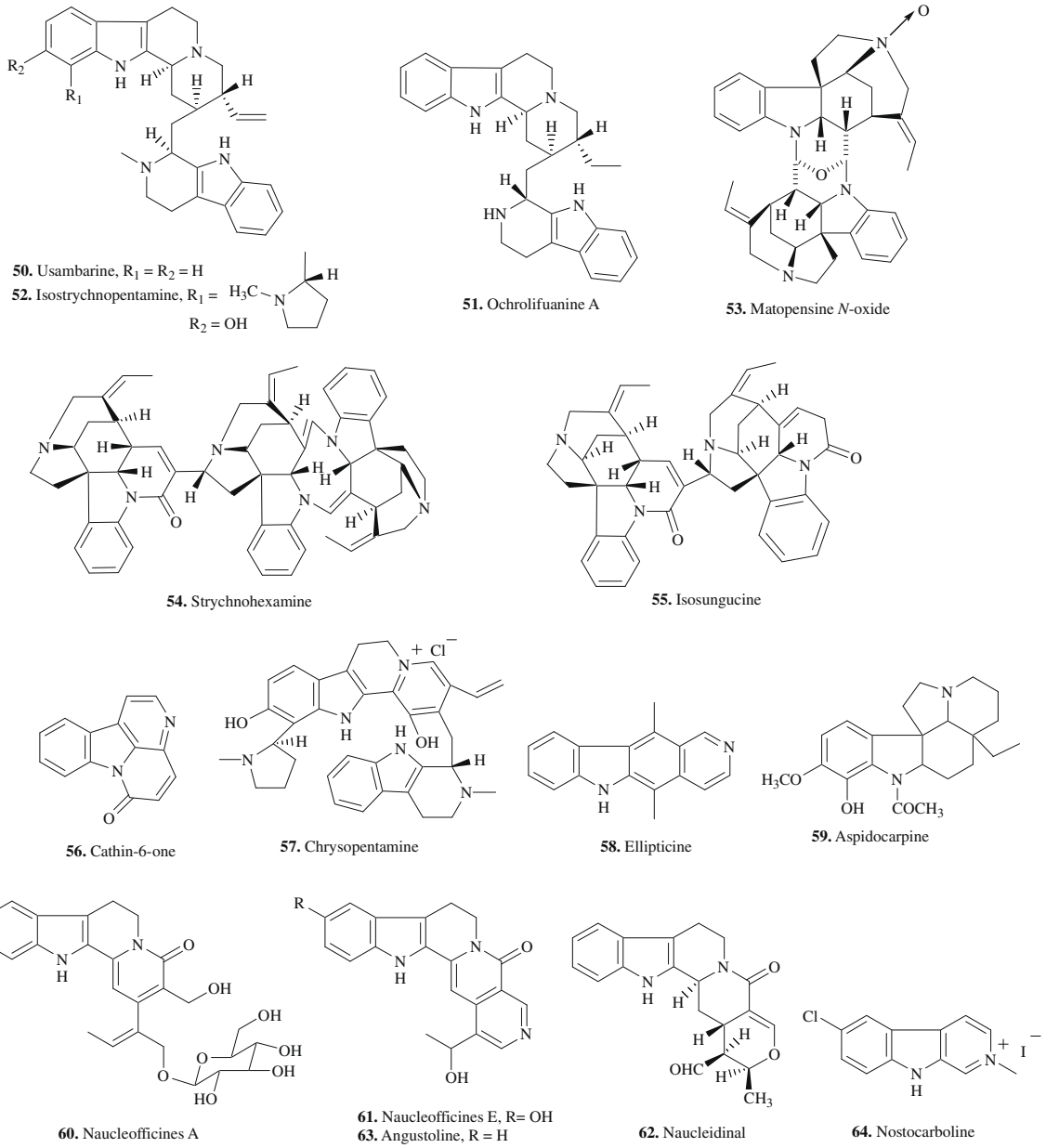


Figure 5. Antimalarial alkaloids.

strychnohexamine (**54**) also possesses antiplasmodial properties in micromolar range. These alkaloids are derivatives of strychnine and due to their potential use as antimalarial drugs Philippe et al. investigated their possible convulsant strychnine-like properties by studying their interaction with the strychnine-sensitive glycine receptor. All compounds interacted with poor efficacy and only at concentrations >1 μM.[50] These studies suggested that promising antimalarial alkaloids derived from *S. icaja* are devoid of strychnine-related properties in vitro. Recently, Philippe et al. have reported *in vivo* antimalarial activity of isosungucine (**55**) a quasi-symmetric bisindolomonoterpenoid isolated from the roots of *S. icaja*, against *P. vinckei petteri* with 50% suppression of parasitemia on day 4 at the dose of 30 mg/kg.[51] Antimalarial β-carboline alkaloids, canthin-6-one (**56**) and 9-hydroxycanthin-6-one (IC_{50} = 2238 and 2336 ng/mL, respectively) were isolated from the roots of *Eurycoma longifolia*.[52]

Chrysopentamine (**57**) isolated from *S. usambarensis* a novel indolomonoterpenoid alkaloid belongs to the small family of indolic anhydronium bases, having five nitrogen atoms, an unusual phenolic substitution on C-14 and a pyridinium ring.[53] Chrysopentamine (**57**) displayed antiplasmodial activity against three *P. falciparum* cell lines FCA 20, FCB1-R and W2 (IC_{50} ~500 nM). Monoterpene indole alkaloids ellipticine (**58**) and aspidocarpine (**59**) isolated from *Aspidosperma vargasii* and *A. desmanthum*, respectively, exhibited significant in vitro inhibition of *P. falciparum* K1 strain, (IC_{50} = 73 and 19 nM, respectively).[54] Tetrahydro-β-carboline monoterpene indole alkaloids isolated from *Nauclea officinalis* were reported to have in vitro antimalarial activity.[55] Naucleofficine A (**60**) exhibited moderate antimalarial activity (IC_{50} = 9.7 μM), and was not cytotoxic. When the aromatic hydrogen of ring A (position 10 or 12) were replaced, the antimalarial activity (IC_{50} = 38.3 μM) was reduced for naucleofficine E (**61**). When ring D was aromatic, the antimalarial activity increased; however when all the rings (ring A–E) were aromatic, the antimalarial activity decreased.

Naucleidinal (**62**) and angustoline (**63**) displayed good cytotoxic activities, but poor antimalarial activity (IC_{50} = 26.8 and 20.5 μM, respectively). Therefore, the antimalarial activity of these compounds had no direct correlation with their cytotoxicity. These results showed that no replacement group in ring A, an aromatic ring D and proper water-solubility are important for antimalarial activity. The quaternary β-carbolinium alkaloid nostocarboline (**64**) from the cyanobacterium *Nostoc* 78-12A showed pronounced activity (IC_{50} = 194 nM) with high selectivity (600-fold) for *Plasmodium* over rat myoblast (L6 cells).[56] Alkaloid **64** targets the plastid-like organelle of the parasite called apicoplast.

3.5. Manzamine alkaloids (Fig. 6)

Enantiomers of 8-hydroxymanzamine A, manzamine F and a manzamine dimer, *neo*-kauluamine (**65**), possessing antiplasmodial activities were isolated from Indo-Pacific sponge (*Petrosiidae*).[57] *ent*-8-Hydroxymanzamine A (**66**) and *neo*-kauluamine (**65**) reduced parasitemia in *P. berghei* infected mice without toxicity at 100 μmol/kg and increased the survival days to 9–12 days as compared to artemisinin (2 days) and chloroquine (6 days). The increase in survival days appears to be attributed to immunestimulatory effect of these alkaloids. Rao et al. reported antimalarial activities and SAR of manzamine-type alkaloids isolated from an Indonesian *Acanthostrongylophora* sponge.[58] Oxamanzamines like 12,28-oxaircinal A (**67**) possessing a unique manzamine-type aminal ring system generated through an ether linkage were inactive against *P. falciparum*, suggesting that the C-12 hydroxy, the C-34 methine, or the conformation of the lower aliphatic rings play a key role in the antimalarial activity. The activity of manzamine Y (**68**, IC_{50} = 420 ng/mL) was lower than 8-hydroxymanzamine A (**69**, IC_{50} = 6.0 ng/mL) indicating that the change of the hydroxyl substitution from C-8 position of the β-carboline moiety to the C-6 position decreases the antimalarial activity.

3.6. Miscellaneous alkaloids (Figs. 6 and 7)

Elena et al. tested crude extracts from *Peschiera fuchsiaefolia* against *P. falciparum*. The tertiary alkaloid crude extract from the stem bark and root bark showed good activity (IC_{50} = 495 and 179 ng/mL, respectively). The dimeric voacamine (**70**) was the most active alkaloid isolated from these extracts (IC_{50} = 238 ng/mL).[59] Wright et al. reported an extensive study on two novel alkaloids, lepadins E (**71**) and F (**72**) isolated from a tropical marine tunicate *Didemnum* sp., which showed significant antiplasmodial activity (IC_{50} = 0.4 and 0.2 μg/mL against K1 strain, and 0.9 and 0.3 μg/mL against NF54 strain, respectively).[60] The activity appeared to be dependent on the configuration at C-2 and the nature of the functionality at C-3 in the decahydroquinoline. Heptyl prodigiosin (**73**), a trypyrrole alkaloid purified from the culture of a proteobacteria from a marine tunicate in the Philippines, was subjected to in vitro and in vivo antimalarial studies.[61] The in vitro activity against *P. falciparum* 3D7 was similar to chloroquine (IC_{50} = 0.07 vs 0.015 μM, respectively) and a single subcutaneous administration of 5.0–20.0 mg/kg significantly extended survival of *P. berghei* ANKA strain-infected mice.

Crude MeOH extracts from the stem bark and leaves of *Albizia adinocephala* were found to inhibit the malarial enzyme plasmepsin II. Bioassay guided fractionation led to the isolation of two bioactive spermine alkaloids, budmunchiamines L4 (**74**) and L5 (**75**) (IC_{50} = 14.0 and 15.0 μM, respectively).[62] Balansard et al. reported the antimalarial activities of four major alkaloids from *Stephania rotunda*: dehydroroemerine (**76**, IC_{50} = 0.36 μM), tetrahydropalmatine (**77**, IC_{50} = 32.6 μM), xylopinine (**78**, IC_{50} = 52.3 μM) and cepharanthine (**79**, IC_{50} = 0.61 μM).[63] Isobol test for drug interaction of chloroquine and these alkaloids indicated that cepharanthine–chloroquine and tetrahydropalmatine–xylopinine associations were synergistic but cepharanthine–artesunate were additive.

Acridone and furoquinoline alkaloids like tegerrardin A (**80**), arborinine and evoxine isolated from *Teclea gerrardii* possessing moderate antiplasmodial activity (IC_{50} = 12.3–70.6 μM) have been reported.[64] Francoise et al. reported the antiplasmodial activity of girolline (**81**), a 2-aminoimidazole extracted from *Cymbastela cantharella*.[65] The IC_{50} values of girolline (**81**) ranged from 77.0 to 215.0 nM and it was active in vivo at a dose of 1.0 mg/kg/day. The mechanism of action of **81** involves inhibition of parasitic protein synthesis. The aminoimidazole moiety was necessary for the antimalarial activity since the synthetic analogs of two series 5-

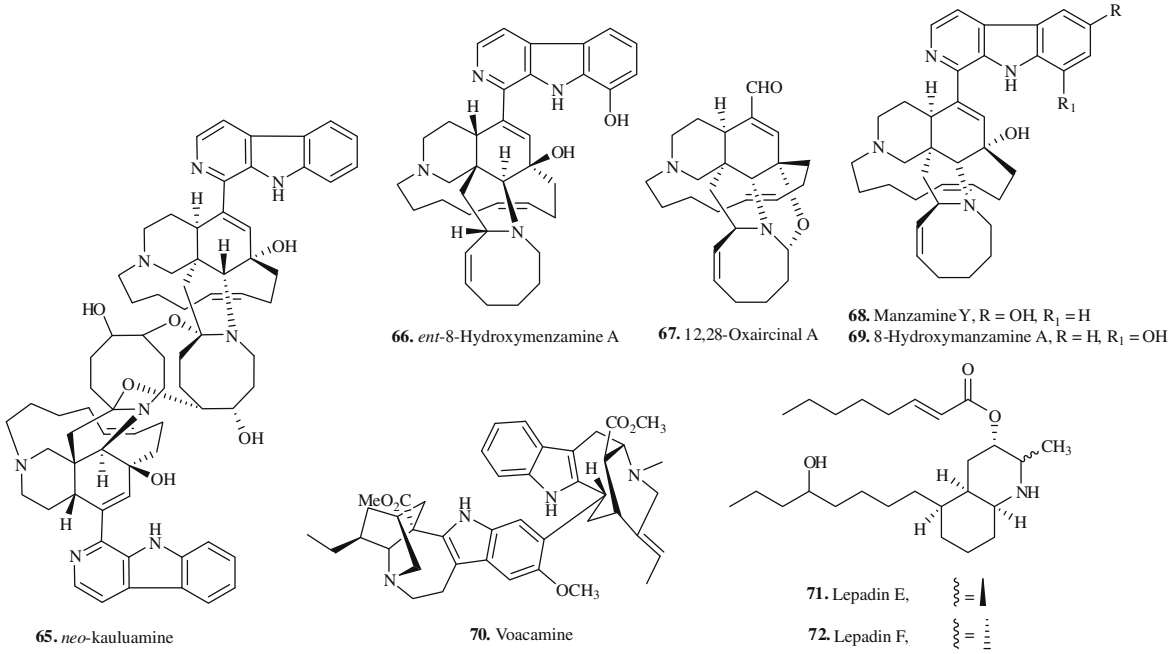
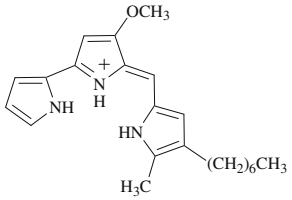
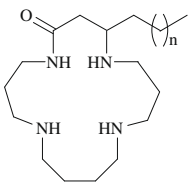


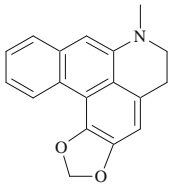
Figure 6. Antimalarial alkaloids.



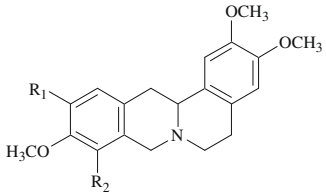
73. Heptyl prodigiosin



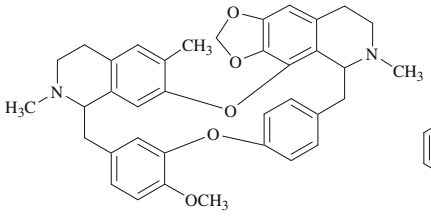
74. Budmunchiamine L4, n = 11
75. Budmunchiamine L5, n = 13



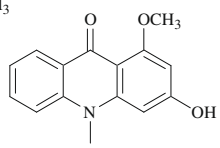
76. Dehydroroemerine



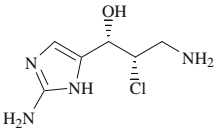
77. Tetrahydropalmatine, R_1 = H, R_2 = OCH_3
78. Xylopinine, R_1 = OCH_3, R_2 = H



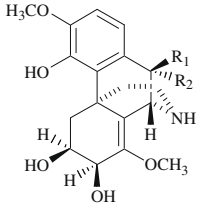
79. Cepharanthine



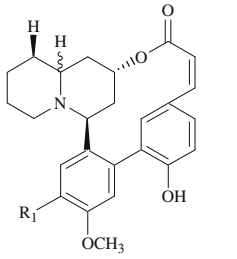
80. Tegerrardin A



81. Girolline



82. Tazopsine, R_1 = OH, R_2 = H
83. Sinococuline, R_1 = R_2 = H
84. 10-*epi*-Tazopsine, R_1 = H, R_2 = OH
85. 10-*epi*-Tazoside, R_1 = H, R_2 = *O*-Glc



86. *epi*-Lyfoline, R_1 = OH,
87. Lyfoline, R_1 = OH,
88. Vertine, R_1 = OCH_3,

Figure 7. Antimalarial alkaloids.

deazathiogirolline and 4-deazathiogirolline, without the aminoimidazole moiety were devoid of any activity.

Morphinan alkaloids tazopsine (**82**), sinococuline (**83**), 10-*epi*-tazopsine (**84**) and 10-*epi*-tazoside (**85**) were obtained from the bioassay-guided fractionation of *S. thouarsii* stem bark extracts.[66] Compounds **82**–**84** exhibited significant and selective inhibitory activity (SI > 13.8) against *P. yoelii* liver stage. Tazopsine (**82**) showed the moderate inhibitory activity (IC_{50} = 3.1 μM), while 10-*epi*-tazopsine (**84**) was fivefold less active and less toxic on host cells than **82**, with better selectivity index (SI = 24.1). These results suggested that substitution at C-10 position was not necessary for the antimalarial activity. The presence of a free hydroxyl group with (*R*)-stereochemistry enhanced the inhibitory effect against *P. yoelii* liver stage, while presence of (*S*)-stereochemistry decreased significantly the toxicity on host mouse primary hepatocytes. The linkage of this hydroxyl group with a glucose unit via a β-glucosidic bond led to loss in activity. This could be attributed to the steric bulk created by the glucose unit. A total inhibition was observed for **82** at a concentration as low as 7.1 μM, whereas *P. yoelii* parasites could still be observed in cultures treated with high concentrations of reference drug primaquine (38.6 μM of primaquine only inhibited 80% of parasites). Alkaloids belonging to biphenylquinolizidine lactone class were isolated from *Heimia salicifolia*. *epi*-Lyfoline (**86**) exhibited moderate antimalarial activity against *P. falciparum* (IC_{50} = 2.8 μg/ mL), while lyfoline (**87**) with 10-H_α was found to be inactive.[67] Vertine (**88**) was less active (IC_{50} = 4.76 μg/mL), and differs from compound **86** in having methoxy at C-4″. The decrease in potency of **88** can be attributed to methoxy pattern in quinolizidine alkaloids.

4. Terpenes

4.1. Sesquiterpenes (Figs. 8 and 9)

Antimalarial activity of sesquiterpene lactones from *Neurolaena lobata* has been documented.[68] Germacranolide sesquiterpenes, like neurolenin B (**89**, IC_{50} = 0.62 μM) were found to be more potent than furanoheliangolides lobatin B (**90**, IC_{50} = 16.51 μM). Among the germacranolides, the shift of the double bond from the 2,3-position (neurolenin B) into the 3,4-position (lobatin A) led to dramatic decrease in the activity suggesting that one of the structural requirements is the presence of α/β-unsaturated keto function. Additionally, a free hydroxyl group at C-8 increased the antiplasmodial activity, while a free hydroxyl group at C-9 decreased the activity.

Bioasay-guided fractionation of the extract from the wood-decayed fungus *Xylaria* sp. BCC 1067 led to the isolation of elemophilane sesquiterpenes (+)-phaseolinone (**91**) and (+)-phomenone (**92**).[69] Sesquiterpenes **91** and **92** known as phytotoxins exhibited promising antimalarial activity (EC_{50} = 0.50 and 0.32 μg/mL, respectively). Goffin et al. investigated the antiplasmodial properties of *Tithonia diversifolia* against three strains of *P. falciparum*, and sesquiterpene lactone tagitinin C (**93**) was found to be active against FCA strain (IC_{50} = 0.33 μg/mL).[70] Antiplasmodial merosesquiterpene, isocochlioquinone A (**94**, IC_{50} = 1412 ng/mL) from fungus *Drechslera dematioidea*[71] and brominated sesquiterpene (8R^*)-8-bromo-10-*epi*-β-snyderol (**95**, IC_{50} = 2700 ng/mL) from the red alga *Laurencia obtusa*[72] have been reported. Jenett-Siems *et al.* reported four sesquiterpenes, vernodalol, 11β,13-dihydrovernodalin,

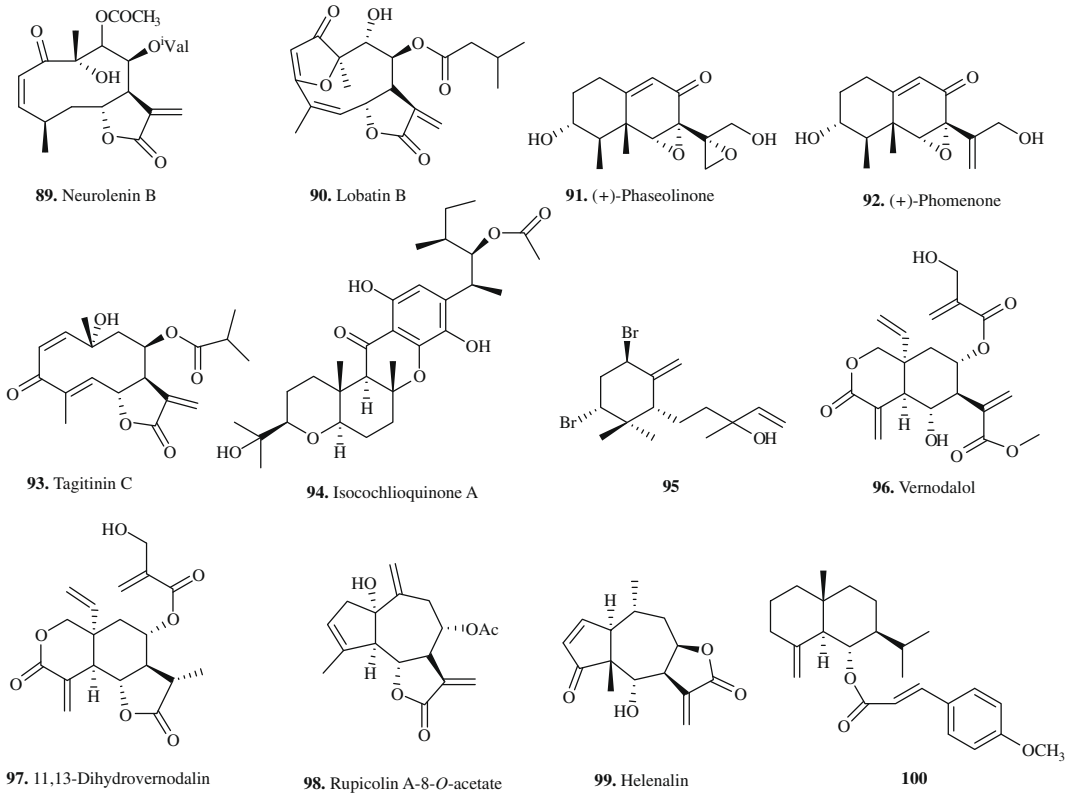


Figure 8. Antimalarial terpenes.

11β,13-dihydrovernolide and 11β,13,17,18-tetrahydrovernolide from *Vernonia colorata*. Of these, vernodalol (**96**) and 11β,13-dihydrovernodalin (**97**) exhibited the strongest antiplasmodial activity (IC_{50} = 4.8 and 1.1 μg/mL, respectively). Among the sesquiterpene lactones obtained from *Artemisia afra*, 1-desoxy-1α-peroxy-rupicolin A-8-*O*-acetate, 1α,4α-dihydroxy-bishopsolicepolide and rupicolin A-8-*O*-acetate (**98**) possessed in vitro antiplasmodial activity (IC_{50} = 10.8–17.5 μg/mL).[73] Passreiter et al. have isolated sesquiterpene lactones of the pseudoguaianolide type from *Arnica montana*. Helenalin (**99**), dihydrohelenalin and their acetates showing activities against *P. falciparum* in vitro with IC_{50} values ranging from 0.23 to 7.41 μM.[74] Several existing antimalarials act by inhibiting the degradation of hemin, leaving it free to kill the malaria parasite. Some eudesmane sesquiterpenes, for example, **100** from the EtOAc extracts of the leaves of *Melampodium camphoratum* have been reported to show activity in the hemin degradation assay.[75] New secondary metabolites belonging to different types of sesquiterpenes, including elemane, eudesmane (**101**) and germacrane (**102**) isolated from Caribbean Coral *Eunicea* sp. were active against *P. falciparum* W2 strain (IC_{50} = 10.0 and 14.0 μg/mL).[76] Inhibitory effect upon the growth of *P. falciparum* has been reported for sesquiterpene lactones **103** and **104** isolated from *Camchaya calcarea* (IC_{50} = 1.2 and 0.3 μg/mL, respectively).[77]

Three linear sesquiterpene lactones obtained from *Anthemis auriculata*, namely anthecotulide (**105**), 4-hydroxyanthecotulide (**106**) and 4-acetoxyanthecotulide (**107**) were evaluated for specific inhibitory effects against the FabI enzyme from three pathogenic microorganisms, *P. falciparum* (PfFabI), *Mycobacterium tuberculosis* (MtFabI) and *Escherichia coli* (EcFabI), and two elongation enzymes from the plasmodial FAS-II system, β-ketoacyl-ACP reductase (PfFabG) and β-hydroxyacyl-ACP deydratase (PfFabZ). The compounds showed clear differentiation in inhibition of FabI enzymes from different species. The oxygenated derivatives (**106** and **107**) specifically inhibited plasmodial FAS-II enzymes, PfFabI and PfFabG (IC_{50} = 20–75 μg/mL).[78] The PfFabI inhibitory effect of **105** was weak, and was identical to its PfFabG inhibitory potential. Hydroxylation of the compound **105** at C-4 as in **106** resulted in a fivefold increase in PfFabI and a 25% increase in PfFabG inhibitory activity. The replacement of the OH group with an acetoxy function at C-4 position, as in **107** only moderately affected PfFabI inhibition, but improved the activity against PfFabG compared to **106**. Thus, it appears that oxygenation of the C-4 position of anthecotulide increases specificity across PfFabI and PfFabG. Notably, the in vitro antimalarial activities of all three compounds were better compared to their PfFAS-II enzyme inhibitory activity, indicating that FAS-II system is not the sole antimalarial target for anthecotulides, and other mechanisms may be also involved.

4.2. Triterpenes (Fig. 9)

Fanta *et al.* reported the antiplasmodial activity of two triterpenoid saponins, glinoside A (**108**) and glinoside B (**109**) isolated from the aerial parts of *Glinus oppositifolius*.[79] The crude extracts exhibited better antiplasmodial activity (IC_{50} = 31.8 μg/mL) than the pure saponins (**108**, IC_{50} = 42.3 μg/mL). An antimalarial tirucalla-type triterpene, *epi*-oleanolic acid (**110**, IC_{50} = 28.3 μM) has been reported from *Celaenodendron mexicanum*.[80] Iridal (**111**), a triterpenoidic compound extracted from *Iris germanica* L. showed IC_{50} values ranging from 1.8, 26.0 and 14.0 μg/mL against *P. falciparum* for three incubation times (72 h, 48 h and 32 h, respectively).[81] IC_{50} values for Iridal (**111**) were lower after 72 h than after 32 or 48 h, which suggested that this compound is probably more active in the reinvasion step than in the maturation step of *P. falciparum* and has cumulative effect on the main metabolic pathways of the parasite. The IC_{50} values obtained with the three strains of *P. falciparum* showed no correlation between chloroquine

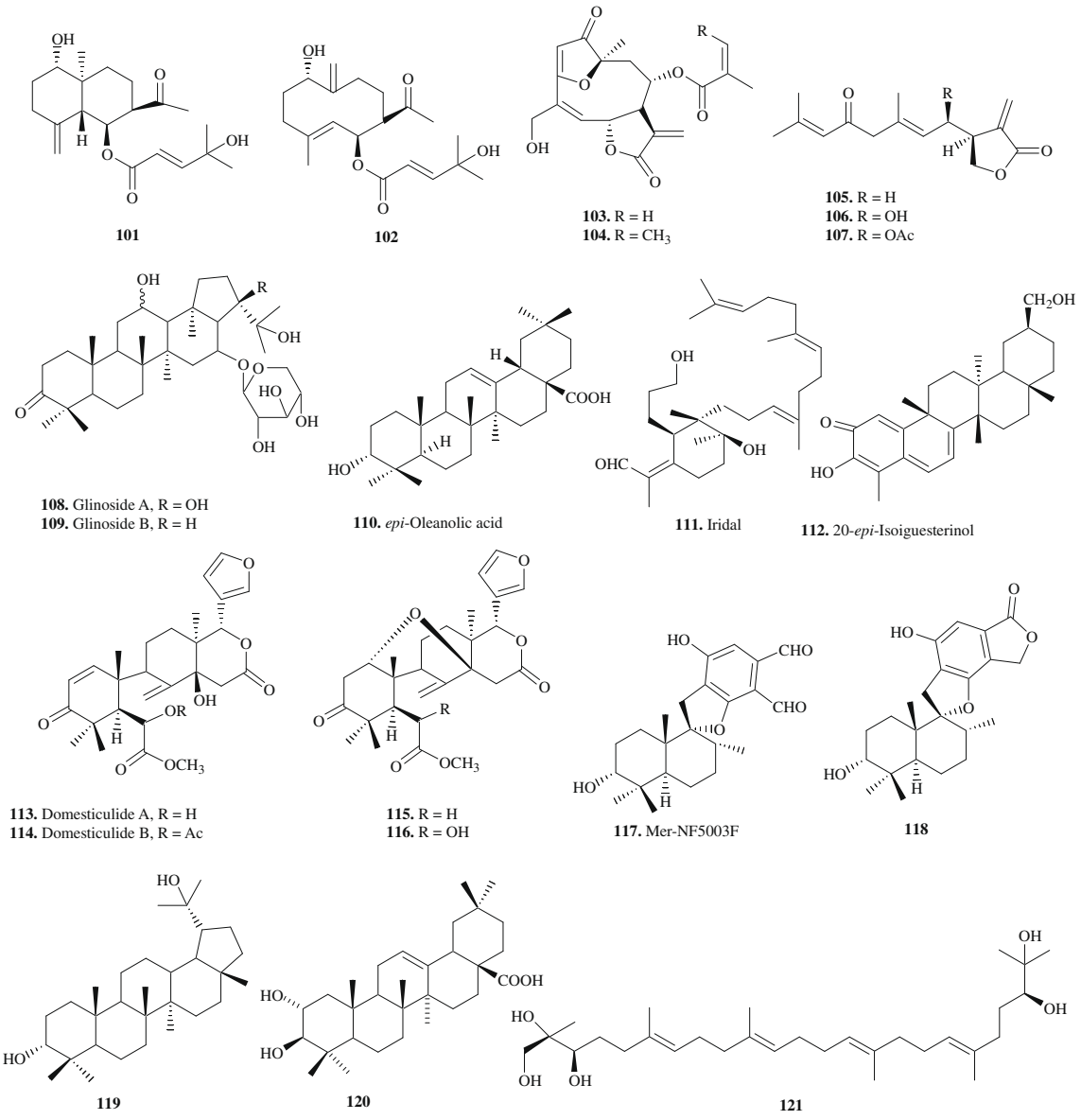


Figure 9. Antimalarial terpenes.

and iridal sensitivity, indicating that the modes of action of iridal and chloroquine should be different. A bisnortriterpene quinone methide, 20-*epi*-isoiguesterinol (**112**) isolated from the roots of *Salacia madagascariensis* showed potent activity against *P. falciparum* (IC_{50} = 68 ng/mL).[82] Saewan et al. reported antimalarial activity of tetranortriterpenoids, domesticulide A (**113**) and domesticulide B **(114)** and triterpenoids (**115**, **116**), isolated from the seeds of *Lansium domesticum* Corr.[83] Comparison of activities of triterpenoids **115** and **116** suggested that the addition of a hydroxyl function at C-6 considerably decreases the antimalarial activity (IC_{50} = 5.9 and >20 μg/mL, respectively), but in tetranortriterpenoids the substitution of an acetoxyl group in the place of a hydroxyl group at C-6 resulted in higher activity (**113**, IC_{50} = >20 μg/mL, and **114**, IC_{50} = 3.2 μg/mL). Antimalarial activity of spirofuran terpenes was reported for the first time by Kittakoop et al.[84] Both spirodihydrobenzofuran terpenes Mer-NF5003F (**117**) and **118** isolated from the fungus *Stachybotrys nephrospora* possessed antiplasmodial activity (IC_{50} = 0.85 and 0.15 μg/mL, respectively) and were not toxic in Vero cell line. The crude extract from *Grewia bilamellata* showed antimalarial activity (IC_{50} = 2.2 and 1.7 μg/mL, D6 and W2 strains).[85] Antimalarial assay guided fractionation led to the isolation of several compounds including two triterpenoids 3α,20-lupandiol (**119**, IC_{50} = 19.8 μM) and 2α,3β-dihydroxyolean-12-en-28-oic acid (**120** IC_{50} = 21.1 μM). Recently, Murata *et al.* have reported the antiplasmodial activities of acyclic triterpenoids *from Ekebergia capensis* as exemplified by **121** (IC_{50} = 7.0 μM).[86]

4.3. Diterpenes (Fig. 10)

Tilley et al. performed molecular modeling studies on a series of diterpene isonitriles and isothiocyanates isolated from the tropical marine sponge *Cymbastela hooperi*, employing 3D-QSAR with receptor modeling methodologies.[87] These studies showed that the modeled compounds like diisocyanoadociane (**122**) and axisonitrile-3 (**123**) exert their activities by: (i) inhibiting the decomposition of H_2O_2, (ii) inhibiting the peroxidative destruction of FP, and the GSH-mediated breakdown of FP, and (iii) interfering with β–hematin formation. Diisocyanoadociane (**122**) displayed IC_{50} of 14.48 nM against *P. falciparum* D6 strain.

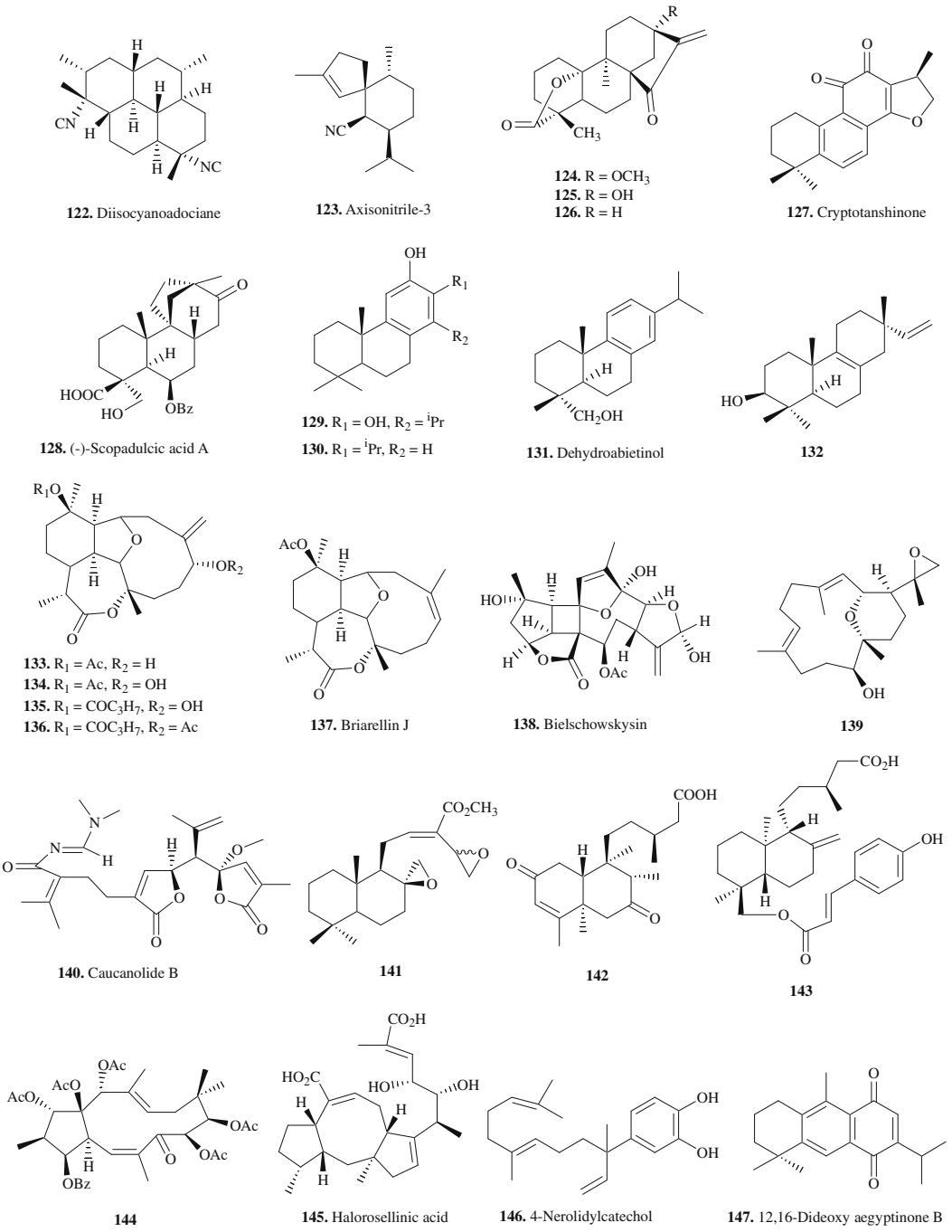


Figure 10. Antimalarial terpenes.

Three diterpene lactones isolated from *Parinari capensis* **124**, **125**, and **126** showed promising antimalarial activity (IC_{50} = 0.54, 0.67, and 1.57 μg/mL, respectively).[88] Although antimalarial activity is promising, the toxicity profiles of these diterpene lactones prevent further biological evaluation. Nevertheless, they are substantially different from existing antimalarials in structure, and may thus be potentially useful leads for a new class of antimalarial drugs. Tanshinones, a group of red pigment are chemically 20-norditerpenes with an abietane-type skeleton containing a quinone moiety in the C-ring. Sairafianpour et al. studied tanshinones exhibiting good antimalarial activity like cryptotanshinone (**127**, IC_{50} = 12.5 μM) from the dried root of *Perovskia abrotanoides*.[89] From the phytochemical screening of *Scoparia dulcis* a tetracyclic diterpene acid, (-)-scopadulcic acid A (SDA, **128**) had shown activity against *P. falciparum* (IC_{50} = 27.0 and 19.0 μM, D6 and W2 strains, respectively).[90] The mechanism of action of **128** was thought to be related to inhibition of H^+-ATPase pumps present in the plasma membrane and food vacuole of the parasite. Clarkson *et al.* studied the effect of two diterpenes **129** and **130** isolated from *Harpagophytum procumbens*, on erythrocyte shape to determine the selectivity of their antiplasmodial activity.[91] It was observed that **129** and **130** did not alter erythrocyte shape at the concentrations which resulted in the inhibition of parasite growth (0.76 and 0.95 μg/mL, respectively) or at the highest test concentration (100 μg/mL). This suggested that the mechanism of action of these compounds is different from dehydroabietinol (**131**) despite of structural similarities. Ziegler et al. have reported that antiplasmodial activity of **131**, an abietane-type diterpene from *Hyptis*

suaveolens was due to erythrocyte membrane modification.[92] Diterpene **131** inhibited parasite growth (IC_{50} = 25.6 μM) at similar concentrations at which cytotoxicity was observed (IC_{50} = 28.0 μM). Similarly, the antiplasmodial effect of isopimarane **132** isolated from *Platycladus orientalis* has an indirect effect on the erythrocyte host cell because it incorporates into the lipid bilayer in the concentration regions where antiplasmodial activity was observed (IC_{50} = 24.6 μM).[93] Ten new diterpenes of the eunicellin class, briarellins were isolated from the hexane extracts of the gorgonian *Briareum polyanthes*.[94] Briarellins (**133**–**136**) with a Δ^7 exocyclic double bond and an –OR group at C-6, were most active (IC_{50} = 15.0, 9.0, 9.0 and 8.0 μg/mL, respectively). The absence of an –OR group at C-6 led to significant decrease in activity, as observed in briarellin J (**137**), which is inactive. Bielschowskysin (**138**) a highly oxygenated hexacyclic diterpene isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* showed moderate antimalarial activity.[95] Wei et al. have reported moderate antimalarial activity of novel cembradiene diterpenoids isolated from the Caribbean gorgonian octocoral *Eunicea* sp. (**139**, IC_{50} = 15.0 μg/mL).[96] Cembrane diterpenes are characterized by the presence of an unprecedented ether linkage between C2/C12, a diene and epoxide functionalities. Ospina et al. isolated six diterpenoids, caucanolides A–F from the extracts of the gorgonian octocoral *Pseudopterogorgia bipinnata*.[97] One of these metabolites, caucanolide B (**140**) constituted the first example from nature of a secondary metabolite possessing the N^1,N^1-dimethyl-N^2-acylformamidine functionality. The caucanolides showed moderate in vitro antiplasmodial activity against *P. falciparum* (IC_{50} = 15.0–50.0 μg/mL).

Five labdane diterpenoids were isolated through the phytochemical investigation of seeds of *Aframomum zambesiacum*.[98] Antiplasmodial activity of these labdanes was determined against an FCB1 CQ-resistant strain and the least polar compound **141** was the most active (IC_{50} = 4.97 μM). The leaves of *Nuxia sphaerocephala* showed antiplasmodial activity (IC_{50} = 4.2 μg/mL) and its phytochemical studies led to the isolation of seven new diterpenoids including clerodane (**142**) and labdane (**143**) derivatives showing inhibitory activity (IC_{50} = 4.3–21.0 μg/mL).[99] Poly-O-acylated jatrophane diterpene **144**, isolated from *Pedilanthus tithymaloides* has been reported by Sutthivaiyakit et al. to exhibit antimalarial activity (IC_{50} = 3.4 μg/mL).[100]

4.4. Miscellaneous terpenes (Fig. 10)

Chinworrungsee et al. reported the ophiobolane sesterterpene halorosellinic acid (**145**) from the marine fungus *Halorosellinia oceanica* BCC 5149. Ophiobolane sesterterpenes are reported to be metabolites of fungi and insect wax and are not commonly found in nature. The fusion of rings B and C of ophiobolanes always adopts a *trans*-configuration, but the fusion of rings A and B can be either *cis* or *trans*. Terpene **145** displayed moderate antimalarial activity (IC_{50} = 13 μg/mL) against *P. falciparum* K1 strain.[101] A terpenoid phenylpropanoid, 4-nerolidylcatechol (**146**), found in *Pothomorphe peltata* exhibited good parasite inhibition (IC_{50} = 0.67 μM).[54] Recently, Moein *et al.* isolated and characterized a terpene, 12,16-dideoxy aegyptinone B (**147**) from the roots of *Zhumeria majdae*, which exhibited promising antiplasmodial activity (IC_{50} = 1.3 and 1.4 μg/mL against chloroquine sensitive and resistant strains, respectively).[102]

5. Quassinoids (Fig. 11)

Quassinoids are a group of degraded triterpenes found in the family Simaroubaceae. The majority of isolated quassinoids have a C-20 skeleton and δ-lactones, while the few C-19 skeletal type

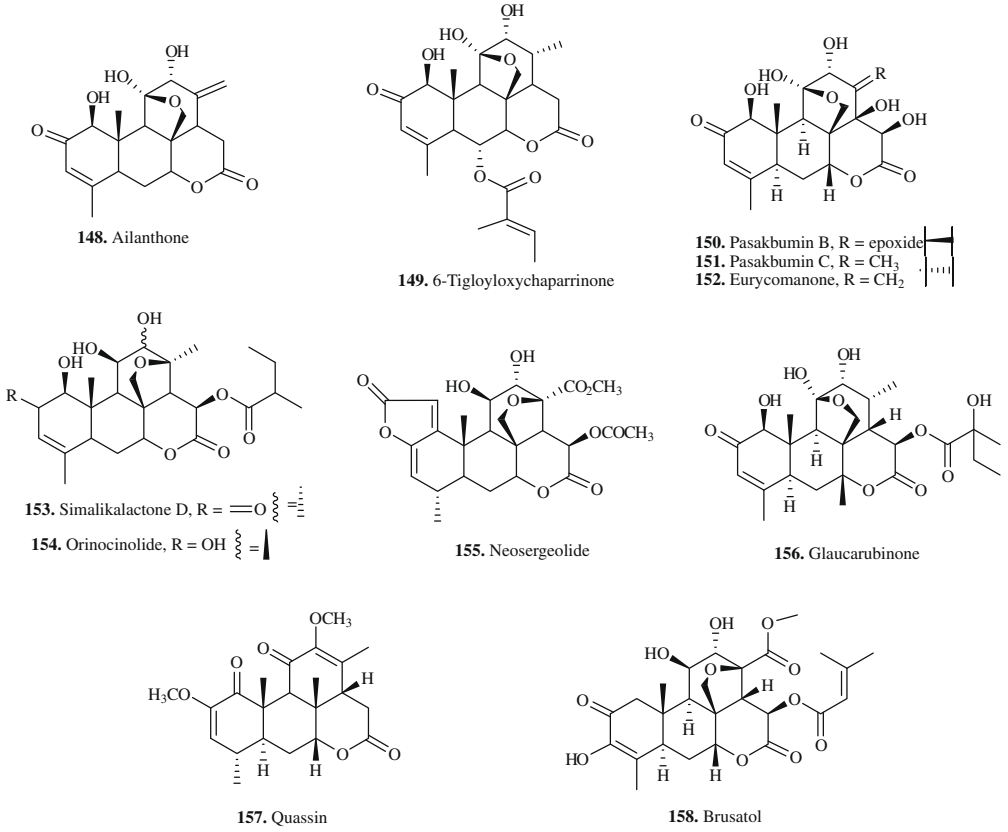


Figure 11. Antimalarial quassinoids.

are γ-lactones. The lactonic linkage may be at C-12 or at C-7. Antimalarial activity has been reported for two quassinoids, ailanthone (**148**, IC_{50} = 0.003 μg/mL) and 6α-tigloyloxychaparrinone (**149**, IC_{50} = 0.061 μg/mL) isolated from *Ailanthus altissima*.[103] Quassinoids like pasakbumin B (**150**), pasakbumin C (**151**) and eurycomanone (**152**) possessing antimalarial activity were isolated from *E. longifolia* (IC_{50} = 22.6, 93.3 and 40.0 ng/mL, respectively).[104,105] Simalikalactone D (**153**) and orinocinolide (**154**) equally potent against D6 and W2 strains (IC_{50} = 3.0 and 3.67 ng/mL vs 3.2 and 8.5 ng/mL, respectively) were isolated from the roots of *Simaba orinocensis*.[106] These quassinoids inhibited protein biosynthesis in vitro in translation system from the Krebs cells. During intraerythrocytic proliferation, the malaria parasite makes its own ribosome, and the selective antimalarial action of these quassinoids may be explained by stronger binding of quassinoids on the parasite ribosomes than binding to the host cell ribosomes. Orinocinolide (**154**) is fourfold less toxic than Simalikalactone D (**153**) and the reduced toxicity is likely due to its reduced inhibitory properties. deAndrade-Neto et al. have reported neosergeolide (**155**) isolated from *Picrolemma sprucei*, showing potent antimalarial activity (IC_{50} = 2.0 nM).[54] Some structural requirements, like presence of α,β-unsaturated ketone in the A ring, an epoxymethylene bridge in the C ring and ester functions in C-15 were considered essential for the antimalarial activity.

Although quassinoids are generally cytotoxic, few compounds such as glaucarubinone (**156**) from *Simarrouba amara* were relatively selective against *P. falciparum* in vitro but were toxic in vivo. SAR studies of a series of quassinoids and structural modifications of quassin (**157**) from *Quassia amara* and brusatol (**158**) a constituent of *Brucea javanica* were carried out in an attempt to improve selectivity against *P. falciparum*. However, these strategies were not successful. The antiplasmodial and cytotoxic properties of the quassinoids are possibly due to protein synthesis inhibition, and it is likely that parasite and host cell ribosomes are too similar to allow for the development of selective inhibitors.[107]

6. Flavonoids (Figs. 12 and 13)

The exact mechanism of antimalarial action of flavonoids is unclear but some flavonoids are shown to inhibit the influx of L-glutamine and myoinositol into infected erythrocytes.[108] Exiguaflavanone A (**159a**) and exiguaflavanone B (**159b**) from *Artemisia indica* exhibited in vitro antiplasmodial activities (IC_{50} = 4.6 and 7.0 μg/mL, respectively).[109] (−)-*cis*-3-Acetoxy-4′,5,7-trihydroxyflavanone (**160**, IC_{50} = 24.3 μg/mL) was isolated from the lipophilic extract of leaves of *Siparuna andina* which showed higher in vitro antimalarial activity (IC_{50} = 3.0 μg/mL).[110] Although obtained from an active fraction, **160** was less active (IC_{50} = 24.3 mg/mL). 6-Hydroxyluteolin-7-*O*-(1″-α-rhamnoside) (**161**, IC_{50} = 2.13 and 3.32 μM against K1 and NF54 strains, respectively) obtained from *Vriesea sanguinolenta*,[111] acacetin (**162**, IC_{50} = 5.5 and 12.6 μg/mL against poW and Dd2 strain, respectively), 7-methoxyacacetin, and genkwanin isolated from *A. afra*,[73] possessed considerable antiplasmodial activity. *Andira inermis* yielded calycosin (**163**) and genistein (**164**), which were the first isoflavones to possess antiplasmodial activity (IC_{50} = 4.2 and 9.8 μg/mL for **163**, and IC_{50} = 2.0 and 4.1 μg/mL for **164**, against poW and Dd2 strains, respectively).[112] Antiplasmodial activities of isoflavanquinones were reported for the first time by Kittakoop et al. through isolation of abruquinone B (**165**, IC_{50} = 1.5 μg/mL) from aerial parts of *Abrus precatorius*.[113] Antimalarial flavonol arabinofuranosides were obtained from the leaves of *Calycolpus warszewiczianus* as exemplified by **166**, IC_{50} = 14.5 μM.[114] SAR studies showed that the galloyl moiety increases antimalarial activity, while acetate group decreases the activity. A flavone glycoside **167** from *Phlomis brunneogaleata*,[115] and iridoid **168** from *Scrophularia lepidota*,[116] have been reported to inhibit FabI enzyme of *P. falciparum* (IC_{50} = 10.0 and 100.0 μg/mL, respectively). Many biflavones have been reported to possess moderate to good antimalarial activity like, sikokianin B and C (**169** and **170**, IC_{50} = 0.54 and 0.56 μg/mL, respectively) from *Wikstroemia indica*,[117] **171** (IC_{50} = 80.0 ng/mL) isolated from *Ochna integerrima*,[118] and **172** (IC_{50} = 6.7 μM) from *Garcinia livingstonei*.[119] Compound **171** was 10 times more active than sikokianin B and C, suggesting that the stereochemistry of the C3/C3″ coupling bond and methoxy substitution might affect activity. Green tea extracts contain a variety of secondary metabolites, mainly flavonoids called catechins, which include (−) epigallocatechin gallate (EGCG), (−)-epicatechin gallate, (−)-epigallocatechin, and (−)-epicatechin. Surolia et al. recently showed that these flavonoids inhibit PfENR reversibly with EGCG (**173**) being the best (K_i = 79 ± 2.67 nM).[120] Additionally, all of them potentiated the binding of triclosan with PfENR by a two step mechanism, thereby increasing the activity of triclosan (K_i = 1.9 ± 0.46 pM).

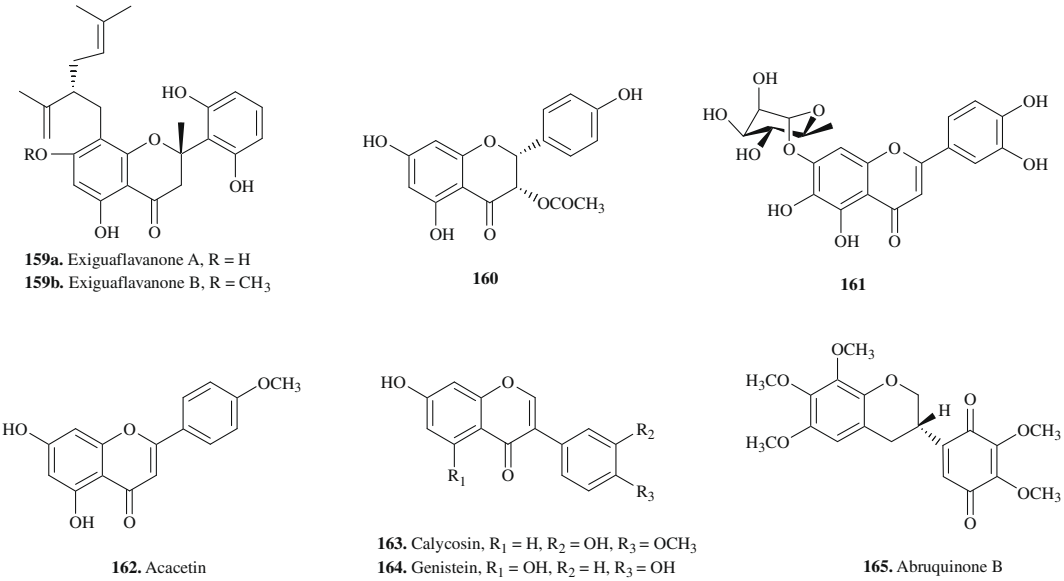


Figure 12. Antimalarial flavonoids.

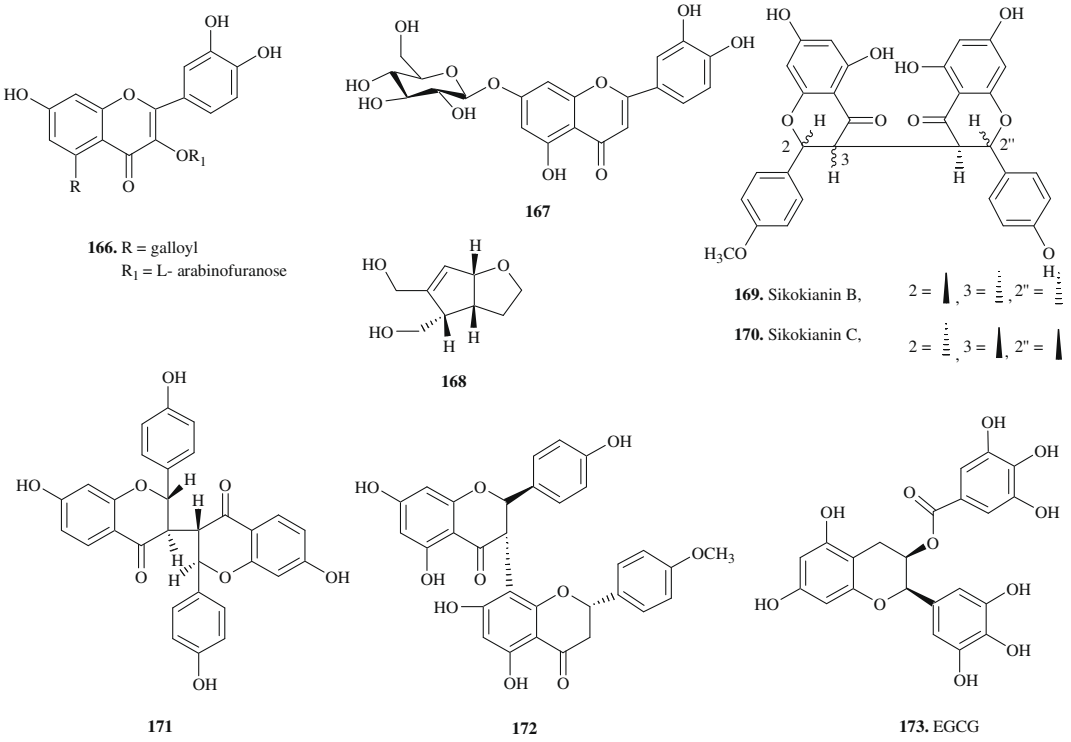


Figure 13. Antimalarial flavonoids.

7. Limonoids (Fig. 14)

Limonoids are produced by species of Meliaceae. One well known representative from this family is *Azadirachta indica*, the Neem tree, widely used as an antiplasmodial plant in Asia. Rochanakij et al. identified nimbolide as the active antimalarial principle of the Neem tree (EC_{50} = 0.95 ng/mL, *P. falciparum* K1).[121] Gedunin (**174**, IC_{50} = 720 ng/mL, *P. falciparum* D6) and its dihydro derivative were also found to be active in vitro (IC_{50} = 2630 ng/mL).[122] Limonoids, which exhibit in vitro antimalarial activities have been reported from *Cedrela odorata*,[123] *Khaya senegalensis*,[124] and *Khaya grandifoliola*.[125] Two limonoids, trichirubine A (**175**) and B (**176**) have been isolated from *T. rubescens* with significant antimalarial activity (IC_{50} = 0.3 and 0.2 μg/mL, respectively).[126] Their antimalarial activities may be related to the presence of reactive groups on ring A like the carbonyl group at C-3 and unsaturation in C-1/C-2 positions. The limonoid derivatives 7-deacetylgedunin (**177**) and 7-deacetyl-7-oxogedunin (**178**) isolated from the roots of *Pseudocedrela kotschyi* have been reported to display moderate antimalarial activity (IC_{50} = 1.36 and 1.77 μg/mL, respectively).[127]

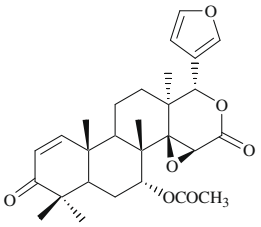
8. Chalcones (Fig. 14)

Licochalcone A (**179**), isolated from *Glycyrrhiza inflata* has been identified as potent inhibitor of protease activities of *Plasmodium*.[128] (+)-Nyasol (**180**, IC_{50} = 49 μM) isolated from *Asparagus africanus*,[129] and pinostrobin (**181**, IC_{50} > 100 μM) from *Cajanus cajan*[130] possess weak antimalarial activity. 5-Prenylbutein (**182**, IC_{50} = 10.3 μM) from *Erythrina abyssinica*,[131] and prenylsubstituted dihydrochalcone **183** (IC_{50} = 5.64 μM) from *Piper hostmannianum*[132] exhibiting antimalarial activity have been reported. Boyom et al. isolated bartericin A (**184**), stipulin (**185**), 4-hydroxylonchocarpin (**186**) from *Dorstenia barteri* var. *subtriangularis*.[133] Compounds **184**–**186** were active in vitro against *P. falciparum* (IC_{50} = 2.15, 5.13 and 3.36 μM, respectively).

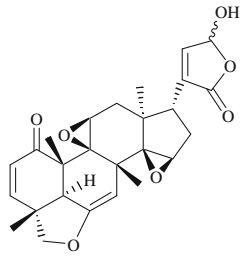
9. Peptides (Fig. 15)

Antiparasitic agent apicidin (**187**), isolated from the cultures of *Fusarium pallidoroseum* belongs to a rare group of cyclic tetrapeptide (CTP) fungal metabolites. Apicidin inhibits protozoal histone deacetylase (HAD) at low nanomolar concentration and is orally active against *P. berghei* in mice.[134] HAD is a key nuclear enzyme involved in the transcriptional control. The continuous acetylation/deacetylation of the ε-amino group of specific histone lysine residues is required for this process, and the inhibition of histone deacetylation interferes with transcriptional control and thus cell proliferation. The 2-amino-8-oxo-decanoic moiety of apicidin presumably mimics the ε-amino acetylated lysine residues of histone substrates, resulting in potent reversible inhibition of HAD.

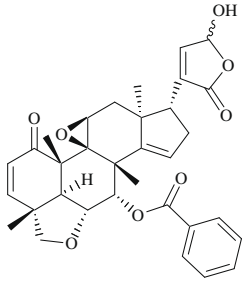
Dermaseptin S4 (ALWMTLLKKVLKAAAKAALNAVLVGANA) and dermaseptin S3 (ALWKNMLKGIGKLAGKAALGAVKKLVGAES) are antimicrobial peptides isolated from frog skin. Ghosh et al. reported that the hemolytic peptide dermaseptin S4 (DS4) and the non-hemolytic dermaseptin S3 (DS3) inhibited the parasite's ability to incorporate [^{3}H]hypoxanthine.[135] DS4 was toxic toward both the parasite and the host erythrocyte, but DS3 was toxic only toward the intraerythrocytic parasite. Two cyclodepsipeptides, beauvericin (**188**) and beauvericin A (**189**) were isolated from the insect pathogenic fungus *Paecilomyces tenuipes* BCC 1614, exhibiting moderate antiplasmodial activities against K1 strain (EC_{50} = 1.60 and 12.0 μg/mL, respectively).[136] Mizuno et al. studied the pharmacology of jasplakinolide (**190**), a cyclic peptide isolated from the marine sponge *Jaspis* sp. Jasplakinolide (**190**) markedly decreased parasitemia of *P. falciparum* by virtue of an apical protrusion that appears to interfere with the erythrocyte invasion by the merozoites and whose mechanism of formation is possibly related to an increase in F-actin content of the merozoites treated with this marine agent.[137] Fennell et al. reported the antimalarial activity of dolastatin 10 (**191**), a peptide microtubule inhibitor isolated from the sea hare *D. auricularia*.[138] Peptide **191** showed



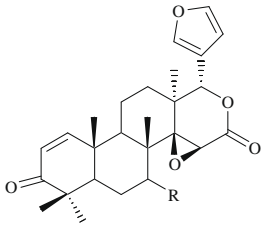
174. Gedunin



175. Trichirubine A

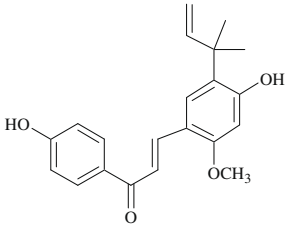


176. Trichirubine B

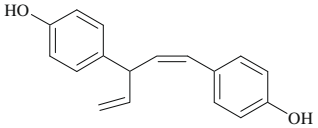


177. 7-Deacetylgedunin, R = ····OH

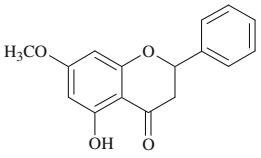
178. 7-Oxo-7- deacetylgedunin, R = =O



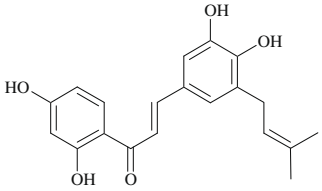
179. Licochalcone A



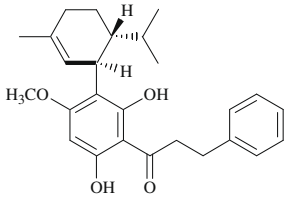
180. (+)-Nyasol



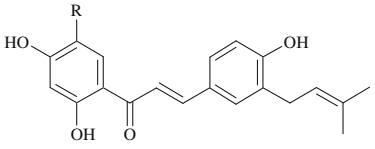
181. Pinostrobin



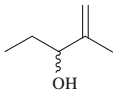
182. 5-Prenylbutein

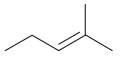


183. (-)-Methyllinderatin

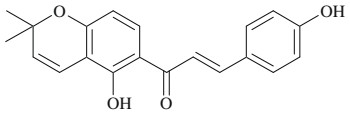


184. Bartericin A, R =





185. Stipulin, R =



186. 4-Hydroxylonchocarpin

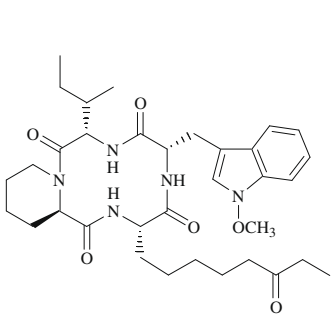
Figure 14. Antimalarial limonoids and chalcones.

potent inhibition of *P. falciparum* (IC_{50} = 0.1 nM) by affecting the schizont stage of intraerythrocytic development, which has the highest concentration of tubulin.

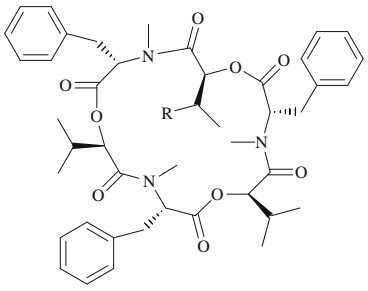
Zimmerman et al. reported a small peptide, CEL-1000 (DGQEEKAGVVSTGLIGGG) derived from the β-chain of the human major histocompatibility complex class II molecule that confers a high degree of protection against *Plasmodium* sporozoite challenge in a murine model. This protection is totally dependent on IFN-γ and partially dependent on $CD4^+$T cells.[139] Hirsutellic acid A (**192**) a linear tetrapeptide isolated from entomopathogenic fungus *Hirsutella* sp. BCC 1528, exhibits activity against *P. falciparum* K1 (IC_{50} = 8.0 μM) without any cytotoxicity to Vero cells.[140] Peptide **192** possesses an anthranilic acid residue at the C-terminal not found commonly in naturally occurring peptides.

Two cyclic hexapeptides, venturamide A (**193**) and venturamide B (**194**) were isolated from the marine cyanobacterium *Oscillatoria* sp. possessing antimalarial activity against W2 strain (IC_{50} = 8.2 and 5.6 μM, respectively), and displayed mild cytotoxicity to mammalian Vero cells (86 and 56 μM, respectively).[141] These are dendroamide-type natural products and represent the first example of cyanobacterial peptides with selective antimalarial activity. Venturamide B (**194**) has a free hydroxyl group, which offers a potential site for derivatization with fluorescent labels to describe the targets of these drugs. Linear alkynoic lipopeptides have been reported from marine cyanobacterium *Lyngbya majuscula*. Carmabin A (**195**), dragomabin (**196**), and dragonamide A (**197**) showed good antimalarial activity (IC_{50} = 4.3, 6.0 and 7.7 μM, respectively), whereas the nonaromatic analog, dragonamide B (**198**) was inactive.[142] The presence of three extra carbons in the aliphatic chain possibly led to the increase in the cytotoxicity of **195** over that of **196**. Lack of activity of **198** suggested that an aromatic amino acid at the carboxy terminus is necessary for antimalarial activity in this series of compounds.

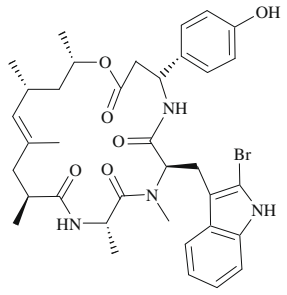
Cyclic hexadepsipeptides, isariin-type and isaridin-type having inhibitory effect on the intra-erythrocytic growth of *Plasmodium* have been isolated from the fungus *Isaria*.[143] The isariins possess



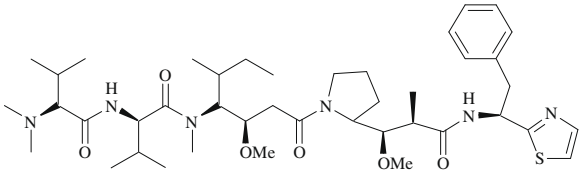
187. Apicidin



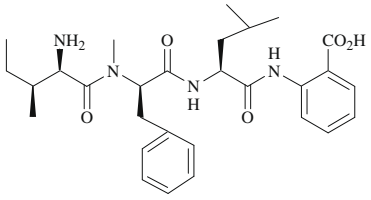
188. Beauvericin, R = CH_3
189. Beauvericin A, R = CH_2CH_3



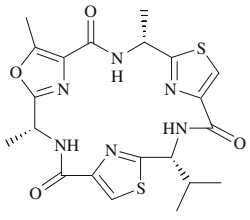
190. (+)-Jasplakinolide



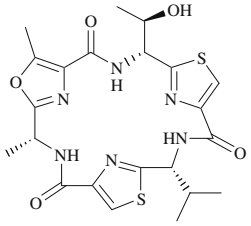
191. Dolastatin 10



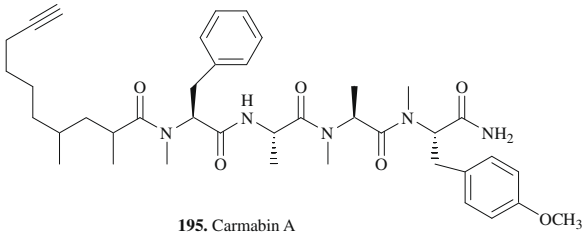
192. Hirsutellic acid



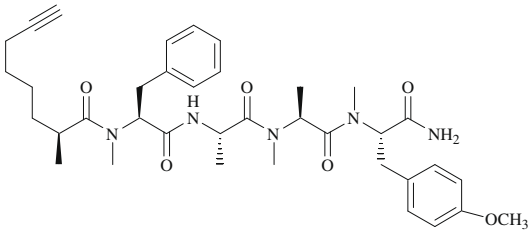
193. Venturamide A



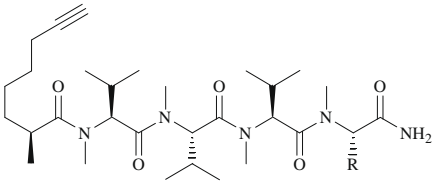
194. Venturamide B



195. Carmabin A



196. Dragomabin



197. Dragonamide A, R = CH_2Ph
198. Dragonamide B, R = ^{i}Pr

Figure 15. Antimalarial peptides.

a β-hydroxy acid residue and five α-amino acids, while isaridins contain a β-amino acid, an α-hydroxy acid, four α-amino acids and a preponderance of N-alkylated residues.

10. Xanthones, quinones and coumarines (Fig. 16)

The *Calophyllum* and *Garcinia* species of the Clusiaceae family are a well-known source of phenolic secondary metabolites, especially xanthones. Antiplasmodial xanthones, cowaxanthone (**199**, IC_{50} = 1.50 μg/mL), calothwaitesixanthone (**200**, IC_{50} = 2.7 μg/mL), and mangostin (**201**, IC_{50} = 17.0 μM), have been reported from *Garcinia cowa*, *Calophyllum caledonicum* and *Garcinia mangostana*, respectively.[144–146] Quinone methides **202** and **203** were isolated from the roots of *Salacia kraussii*. The isolates showed high antiplasmodial activity (IC_{50} = 94.0 and 27.6 ng/mL, respectively).[147] Naphthoquinoid (**204**) and isopinnatal (**205**) possessing good antimalarial activity were reported from *Kigelia pinnata* (IC_{50} = 0.15 and 0.25 μM, respectively).[148] The mode of action of these furano- and hydroxy-naphthoquinones appears to be the inhibition of mitochondrial electron transport and respiratory chain by reduced oxygen consumption similar to that of atovaquone. The lower activity of naphthylisoquinone, plumbagin (**206**, IC_{50} = 0.27 μM) isolated from the roots of *Nepenthes thorelii* than **204** can be due to its annealed ring that decreases electron movement. Its possibility to function as an electron carrier or to trigger a radical formation at the quinone structure is reduced by the presence of OH group. This prevents a possible induction of a parasitocidal oxidative stress resulting in weak efficacy.[149] Phenylanthraquinones like **207** and knipholone (**208**) were isolated from *Bulbine frutescens*. The glycoside **207** displayed better activity than **208** (IC_{50} = 0.41 and 0.67 μg/mL, respectively), whose antiplasmodial activity appears to be associated intrinsically with the complete molecular array of a phenylanthraquinone including the stereogenic axis.[150] Newbouldiaquinone A (**209**) a naphthaquinone–anthraquinone pigment coupled via an ether bridge from *Newbouldia laevis* moderately suppressed growth of *P. falciparum*, in vitro.[151]

Benzoquinone metabolites **210** and **211** from an endophytic fungus *Xylaria* sp[152] have been reported to possess antimalarial

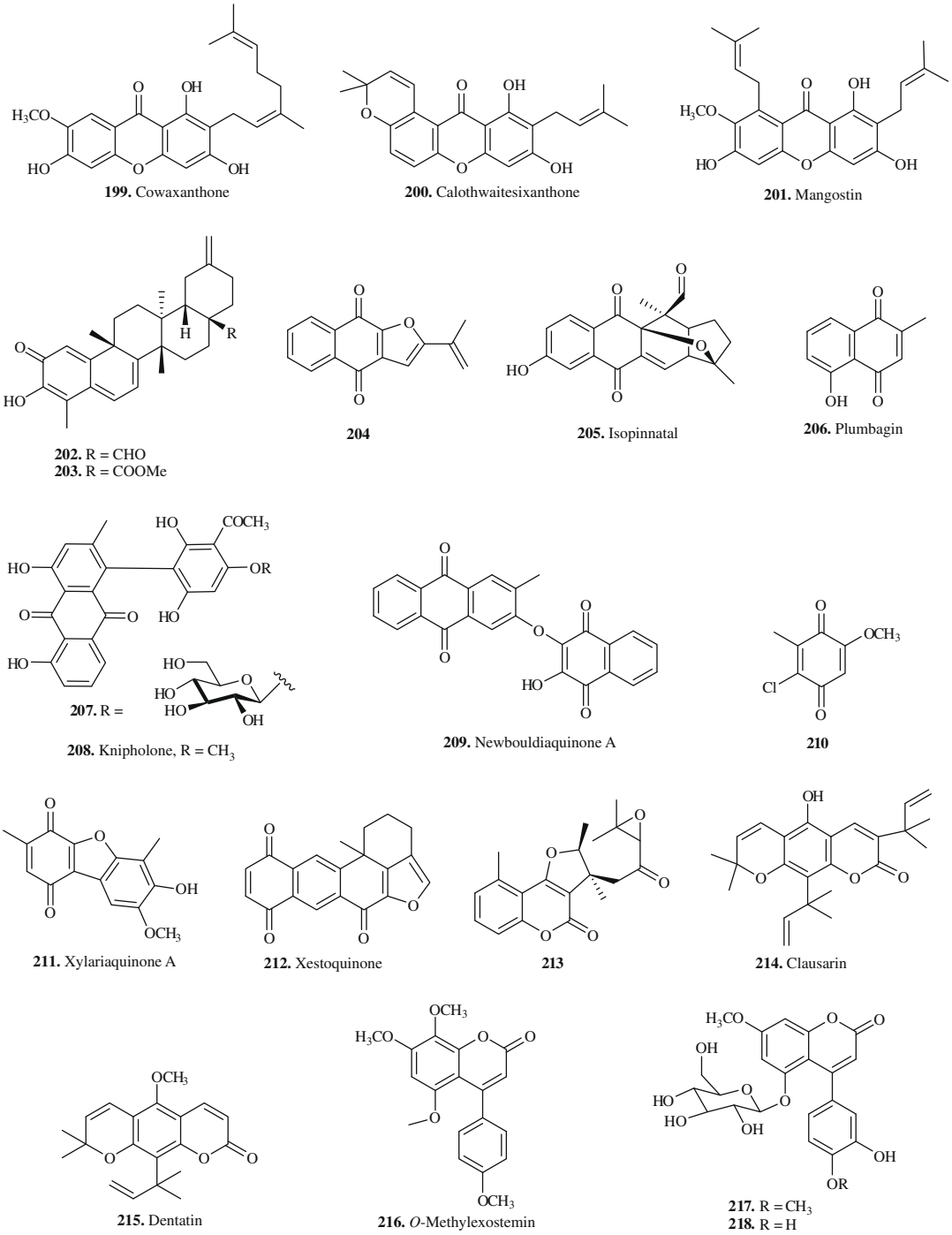


Figure 16. Antimalarial xanthones, quinones and coumarines.

activity (IC_{50} = 1.84 and 6.68 μM, respectively). Laurent et al. isolated xestoquinone (**212**) from marine sponge, *Xestospongia*, which inhibited Pfnek-1 (IC_{50} = 1.1 μM), but was inactive towards PfPK7 and PfGSK-3.[153] Antiplasmodial activity of 2′-epicycloisobrachycoumarinone epoxide (**213**, IC_{50} = 54 μM against Dd2 strain) isolated from *Vernonia brachycalyx*,[154] and clausarin (**214**) and dentatin (**215**) (IC_{50} = 0.1 and 8.5 μg/mL) from *Clausena harmandiana*[155] have been reported.

The stem bark of *Exostema mexicanum* is used as a quinine substitute for malaria treatment in Latin American folk medicine. Bioassay-guided fractionation of lipophilic and hydrophilic extracts from the stem bark yielded 4-phenylcoumarins. The most lipophilic compound, *O*-methylexostemin (**216**) revealed the strongest antiplasmodial activity (IC_{50} = 3.60 μg/mL).[156] The EtOAc extract of the stem bark of *Hintonia latiflora* showed total parasitemia suppression and chemo-suppression of schizont numbers in *P. berghei* infected mice. Antimalarial activity was associated with phenylcoumarins **217** and **218** that suppressed the development of *P. berghei* schizonts in vitro (IC_{50} = 24.7 and 25.9 μM, respectively).[157]

11. Miscellaneous antimalarials from nature (Figs. 17–19)

An aminosteroid, sarachine (**219**) isolated from the leaves of *Saracha punctata* showed strong in vitro antiplasmodial activity (IC_{50} = 25 nM) and in vivo activity against *P. vinckei* (83% inhibition of the parasitemia at 100 mg/kg/2 days).[158] Racemosol (**220**), dem-

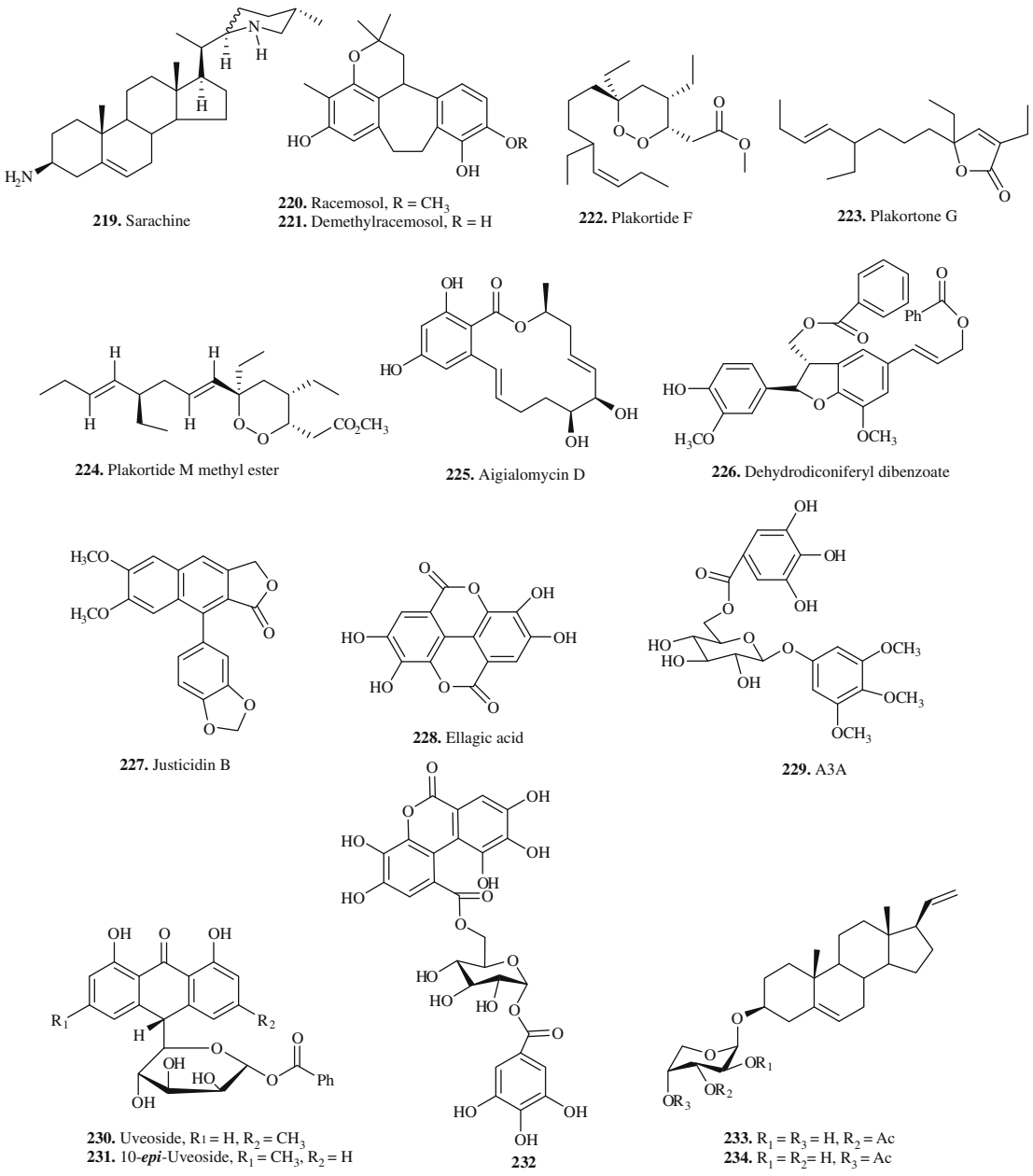


Figure 17. Miscellaneous antimalarials.

ethylracemosol (**221**) and their precursors isolated from the roots of *Bauhinia malabarica*, showed moderate antimalarial activity (EC_{50} = 0.9 and 2.0 μg/mL, respectively) but were cytotoxic against KB and KC cell lines.[159]

A peroxide containing polyketide metabolite, plakortide F (**222**) isolated from the Jamaican sponge *Plakortis* sp. exhibited significant in vitro activity against *P. falciparum* (IC_{50} = 480 and 390 ng/mL, D6 and W2 clones, respectively), however it failed to prolong life expectancy of infected mice at 100 μM/kg.[160] Plakortide F (**222**) and plakortone G (**223**), a lactone isolated from the same sponge, share a common carbon backbone. Compound **223** could result from reduction of the peroxide link in **222**, followed by oxidation at C-1, C-2 and C-3, with subsequent lactonization. This modification in structure results in decrease in activity as **223** is less active than **222**. This suggests that the peroxide bridge is necessary for antimalarial activity. Another polyketide endoperoxide, plakortide M methyl ester (**224**) possessing moderate antiplasmodial activity (IC_{50} = 8.0 μg/mL) has been reported from *Plakortis halichondrioides*.[161] Aigialomycin D (**225**), a 14-membered resorcylic macrolide isolated from the marine mangrove fungus *Aigialus parvus* BCC 5311 displayed antimalarial activity against K1 strain (IC_{50} = 6.6 μg/mL).[162]

Moderate antiplasmodial activities have been reported for 8,5′-linked lignan dehydrodiconiferyl dibenzoate (**226**) (IC_{50} 12.0 μM) isolated from the roots of *Euterpe precatoria*,[163] and an arylnaphthalide lignan justicidin B (**227**, IC_{50} > 5.0 μg/mL) obtained from *Phyllanthus piscatorum*.[164]

Verotta et al. evaluated the plants from New Caledonia with anti-elastase activity for antiplasmodial activity.[165] Elastase is a serine proteinase and aspartic and cysteine proteinases of *Plasmodium* are potential targets for search for new antimalarials. Among the tested plants, *Tristaniopsis* species inhibited parasite growth in vitro. Ellagic acid (**228**) and a glycoside A3A (**229**) were identified as active constituents (IC_{50} = 0.5 and 3.2 μM, respectively). Reduced activity of **229** was attributed to bioavailability. Since gallic acid was inactive it appeared that galloyl and glucose moieties are

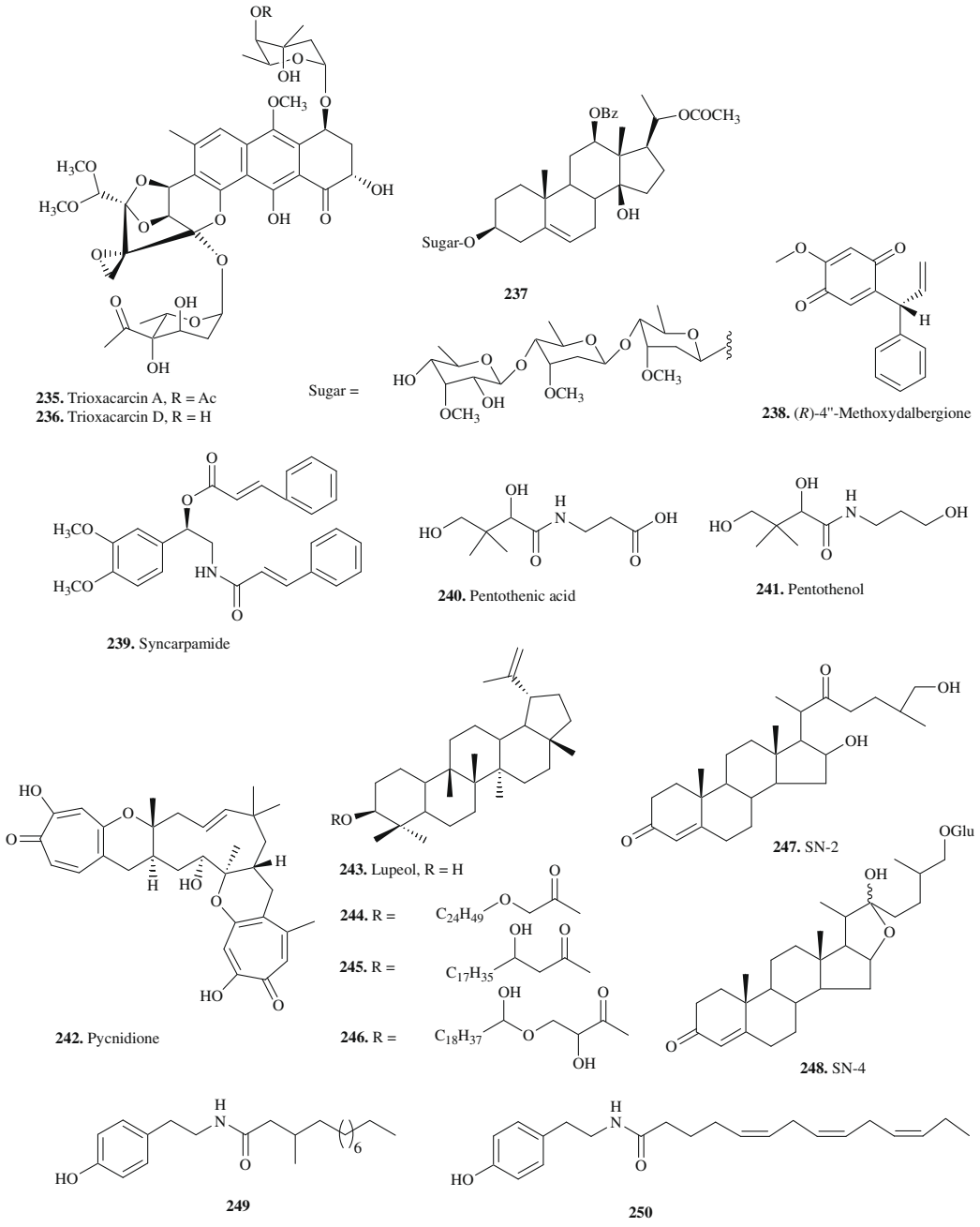


Figure 18. Miscellaneous antimalarials.

devoid of activity and only the trimethoxyphenol group contributed to the observed effect.

Anthrone glycosides uveoside (**230**) and 10-*epi*-uveoside (**231**) isolated from *Picramnia antidesma* have been reported to exhibit good antimalarial activity (IC_{50} = 2.4–5.1 μM) but lacked selectivity.[166] Antiplasmodial activities have been reported for 1-*O*-galloyl-6-*O*-luteoyl-α-D-glucose (**232**, IC_{50} = 1.4 μg/mL) isolated from *Phyllanthus niruri*,[167] and steroidal pregnane glycosides **233** and **234** isolated from the marine octocoral *Muricea austera*.[168] Maskey et al. reported glycosidic trioxacarcins A and D (**235**, **236**) isolated from the marine *Streptomyces* sp. isolate B8652 BCC 5149 possessing high antiplasmodial activity against *P. falciparum* K1 and NF54 strains (IC_{50} = 1.5–1.6 and 2.3–1.7 ng/mL, respectively).[169]

Pregnane glycosides such as **237** possessing moderate antimalarial activity have been isolated from *Caralluma tuberculata* (IC_{50} ranged in 6.25–12.5 μg/mL).[170] A 3,3-diarylpropene derivative, (*R*)-4″-methoxydalbergione (**238**) isolated from *Dalbergia louvelii* displayed modest antimalarial activity (IC_{50} = 5.8 μM).[171] It was observed that the *p*-quinone moiety is essential for the activity since the reduced derivative and O-methylated derivative showed 2–8-fold decrease in the antimalarial potency. Syncarpamide, a (+)-norepinephrine derivative (**239**, IC_{50} = 2.04 and 3.06 μM against D6 and W2 strains, respectively) has been reported from *Zanthoxylum syncarpum*.[172]

Pantothenic acid (**240**), a precursor of the crucial enzyme cofactor coenzyme A, is one of nutrients, which intraerythrocytic parasite requires from the external medium**.** In some organisms and cell types, pantothenol (**241**) is converted (by alcohol dehydrogenase) to pantothenate, and therefore serves as a source of provitamin, **240**. Saliba et al. demonstrated that **241** failed to support parasite growth when substituted for pantothenate in the medium.[173] However, it inhibited growth of *P. falciparum* via a mecha-

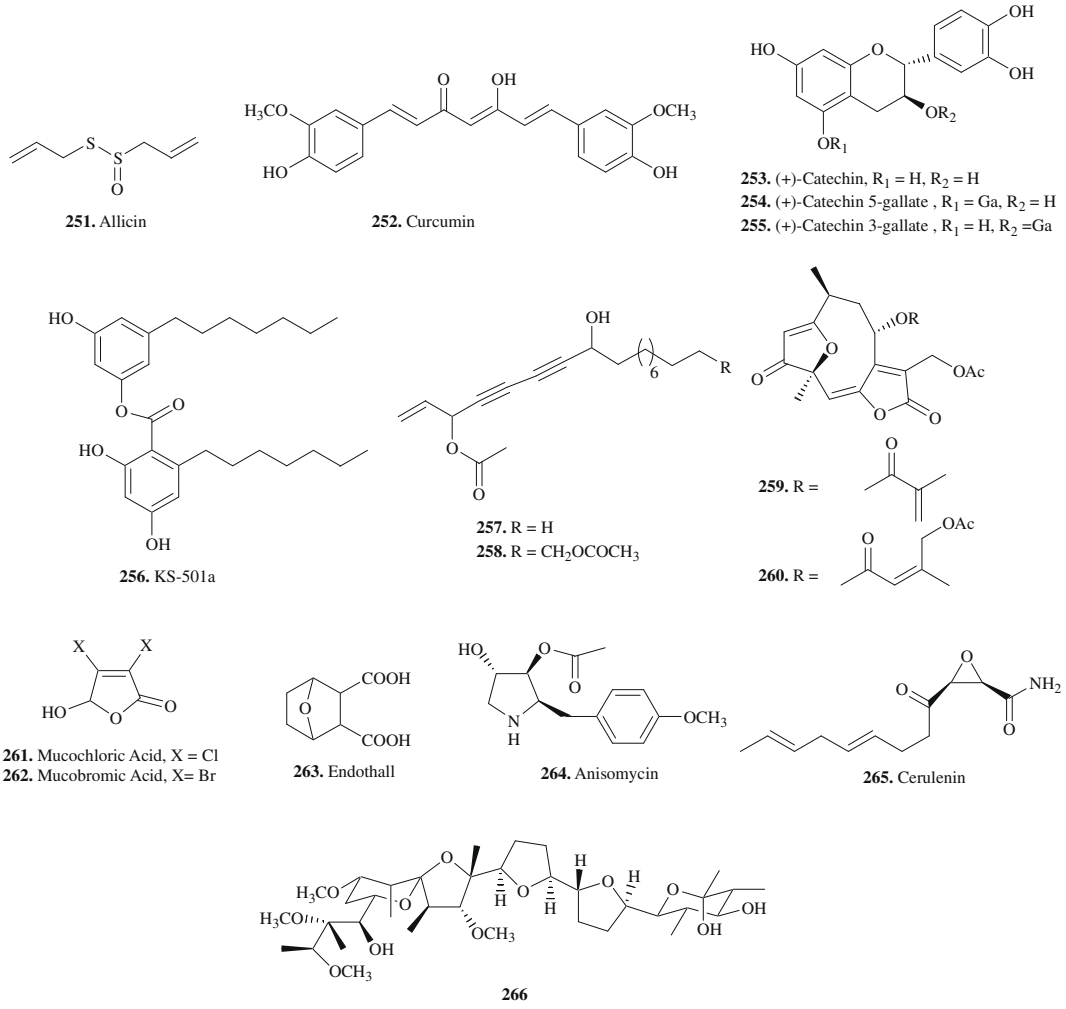


Figure 19. Miscellaneous antimalarials.

nism that involves competition with pantothenate, thus inhibiting the parasite's pantothenate kinase**.** Pycnidione (**242**) a highly oxygenated compound derived from marine fungi was active against three strains of *P. falciparum* FCR3F86, W2 and D6 (IC_{50} = 0.28, 0.37 and 0.75 μM, respectively).[174]

Lupeol (**243**) and its three long-chain fatty acid ester derivatives possessing weak antimalarial activity (IC_{50} = 84.0–269.0 μM) were isolated from the stem bark of *Holarrhena floribunda*.[175] It was found that the most active compound **244** had no hydroxyl group on the side chain, followed by **243** which had no side chain indicating that side chain has a positive effect on antiplasmodial activity. The presence of hydroxyl groups on the side chain decreased the activity, because **245** with one hydroxyl group was less active than **243** and **244** while, **246** having two hydroxyl groups was inactive. Blair et al. have reported antiplasmodial activity of steroidal extracts obtained from *Solanum nudum*.[176] All steroids reduced the number of hepatic *P. vivax* trophozoites; most potent being SN-2 (**247**) and SN-4 (**248**) with 47% and 39% reduction, respectively.

Tyramine derivatives **249** and **250**, exhibiting antimalarial activity (IC_{50} = 45 and 38 μM, respectively) have been isolated from the marine octocoral *Muricea austera*.[168] The major surface protein of *Plasmodium* sporozoites, the circumsporozoite protein (CSP), is proteolytically processed by a parasite-derived cysteine protease, and this event is temporally associated with sporozoite invasion of host cells. Sinnis et al. tested allicin (**251**), a cysteine protease inhibitor found in garlic extracts, for its ability to inhibit malaria infection.[177] At low concentrations, allicin was not toxic to either sporozoites or mammalian cells but inhibited CSP processing and prevented sporozoite invasion of host cells in vitro. In vivo, mice injected with allicin had decreased *Plasmodium* infections compared to controls. When sporozoites were treated with allicin before injection into mice, malaria infection was completely prevented, demonstrating that the same cysteine protease inhibitor can target two different life cycle stages in the vertebrate host.

Curcumin (**252**) is a phenolic diketone and its antimalarial activity has been reported (IC_{50} = 3.5 and 4.2 μg/mL against D6 and W2 strain, respectively).[178,179] Cui et al. demonstrated that the parasiticidal effect of curcumin is due to the generation of reactive oxygen species (ROS) that damage both mitochondrial and nuclear DNA, and down-regulation of the PfGCN5 HAT activity.[180] Phenolic compounds, (+)-catechin (**253**), (+)-catechin 5-gallate (**254**), and (+)-catechin 3-gallate (**255**) were isolated from leaves of *Piptadenia pervillei*.[181] Of these, **254** and **255** displayed the best antimalarial activity (IC_{50} = 1.20 and 1.0 μM, respectively) without any cytotoxicity. The antiplasmodial activity of these compounds appears to be associated with the presence of a gallate ester group, since **253** was inactive. The comparable potency of **254** and **255** showed that the position of galloyl group does not seem to influence the activity. KS-501a (**256**), a phenolic compound exhibiting antimalarial activity against K1 strain (IC_{50} = 9.9 μM) has been reported from the filamentous fungus *Acremonium* sp. BCC 14080.[182] Polyacetylenes **257** and **258**, which possess activity against *P. falci-*

parum have been isolated from *Cussonia zimmermannii* (IC_{50} = 1.4 and 2.2 μM, respectively).[183]

Two hirsutinolides **259** and **260** from *Vernonia staehelinoides* showed in vitro antiplasmodial activity (IC_{50} = 1800 and 2600 ng/mL, respectively) but lacked selectivity.[184] Two main substructures, a 2(5*H*)-furanone unit and a dihydrofuran-4-one were identified as potential pharmacophores, which may be responsible for the antimalarial activity. Two synthetic compounds mucochloric acid (**261**) and mucobromic acid (**262**) were selected as appropriate 2(5*H*)-furanone substructure and were shown to have superior and selective activity against malaria parasite relative to the natural hirsutinolides. The antiplasmodial activities of **261** and **262** (IC_{50} = 137 and 359 ng/mL, respectively) suggested that 2(5*H*)-furanone unit is a key pharmacophore for antiplasmodial activity.

Unlike humans, the malaria parasite has only one enzyme that uses cobalamin as a cofactor, namely methionine synthase, which is important for growth and metabolism. Thus cobalamins in very small amounts are necessary for *P. falciparum* growth but in larger amounts they display antimalarial properties. Chemaly et al. determined the effect of vitamin B12 derivatives on the formation of β-hematin.[185] Adenosylcobalamin (Ado-cbl), methylcobalamin (CH_3-cbl) and aquocobalamin (H_2O-cbl), the major naturally occurring cobalamins in humans, were approximately 40 times more effective inhibitors of β-hematin formation than chloroquine. Cyanocobalamin (CN-cbl, vitamin B12) was also more potent than chloroquine. The antimalarial activity for the cobalamins was found to be less than that for chloroquine or quinine. The cobalamins exert their inhibitory effect on β-hematin formation by π-interactions of their corrin ring with the Fe(III)–protoporphyrin ring and by hydrogen-bonding using their 5,6-dimethylbenzimidazole/ribose/sugar side-chain.

The apicomplexan parasites pathogens such as *Plasmodium* sp. possess an apicoplast, a plastid organelle similar to those of plants. Bajsa et al. examined antiplasmodial activity of some plant synthesized herbicides, phytotoxins and the phytoalexins, with plastid target sites.[186] Endothall (**263**), anisomycin (**264**), and cerulenin (**265**) (IC_{50} = 7.8, 4.6 and 10.1 μM, respectively) had sufficient antiplasmodial action to be considered as new lead antimalarial structures. The antimalarial guided fractionation of the culture of marine *Streptomyces* sp. strain H668 led to the isolation of a new polyether metabolite.[187] Compound **266** showed antiprotozoal activity against both the D6 and W2 clones (IC_{50} = 100–200 ng/mL), and did not show cytotoxicity at 4.75 μg/mL (the highest concentration tested), indicating that it is highly specific to the parasite. Compounds like **266** classified as ionophores owe their potential activity to interact with ions (cations). The mechanism of action for ionophores (quasi-ionophore or mobile carrier) is via alteration of normal membrane permeability to cationic species. They possess polycyclic alkyl backbone, which confers lipophilic character and a terminal carboxyl group and plays an important role in the formation of oxygen rich internal cavity capable of binding metal ions. Since the parasite infected cell membrane is vulnerable to binding with lipophilic compounds, the putative mechanism of action for these polyethers is via transfer of ions through the membrane.

12. Semisynthetic antimalarials

12.1. Semisynthetic alkaloids (Fig. 20)

Bringmann et al. tested a series of natural and structurally modified carbazoles for antimalarial activity.[188] Compound **267** dis-

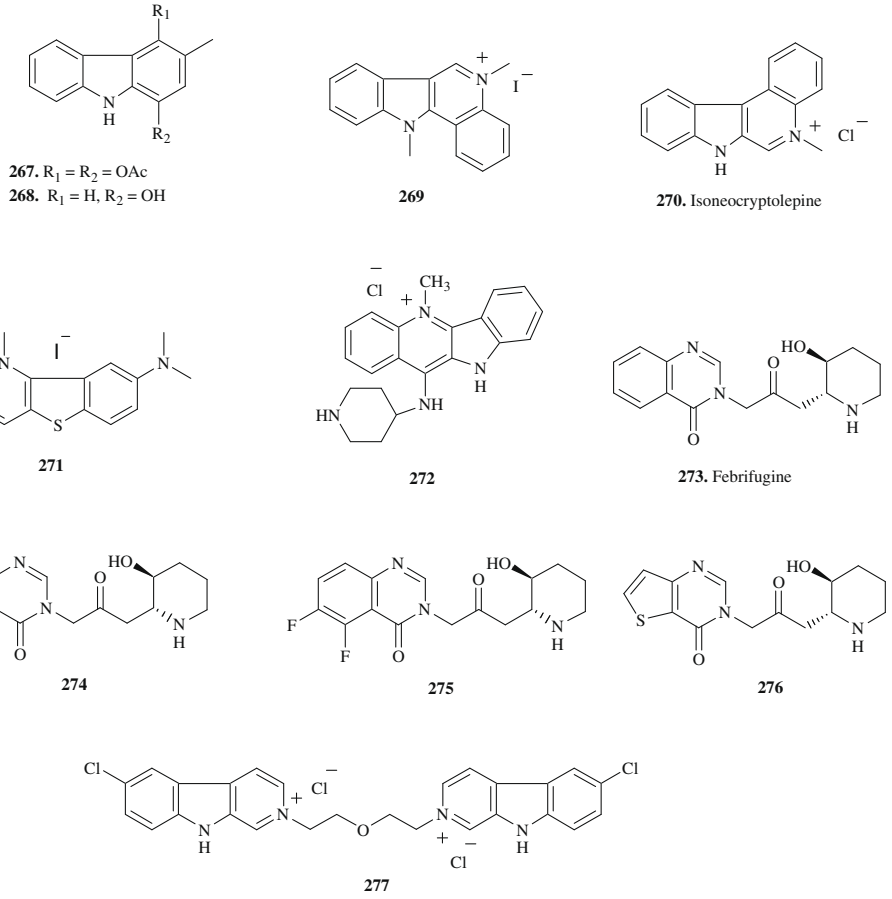


Figure 20. Semisynthetic antimalarial alkaloids.

played the highest activity (IC_{50} = 1.79 μg/mL). It was more active than its dimer, which was the best natural compound **268** in the series, suggesting that a free phenolic hydroxyl function as in **268** is not required for antiplasmodial activity. Cryptolepine (**44**) is a major benzo-δ-carboline alkaloid from shrub *C. sanguinolenta*. Cryptolepine (**44**) and its hydrochloride, display potent in vitro antiplasmodial activity but were cytotoxic that precluded their clinical use. The cytotoxicity can be ascribed to the ability of **44** to intercalate into DNA and inhibit topoisomerase II as well as DNA synthesis. Several synthetic cryptolepine analogs have been reported.[189,190]

Miert et al. synthesized dimethylated indoloquinoline derivative, *N*-methyl-isocryptolepinium iodide (**269**) and isoneocryptolepine (**270**), to compare their biological activities with the naturally occurring cryptolepine.[191] The quaternary alkaloid **269** was 13.5 times more active and selective than **270** in vitro (IC_{50} = 0.017 and 0.23 μM, respectively). Compounds were also evaluated in vivo in mice infected with *P. berghei*. Analog **269** failed to show significant in vivo activity possibly because of its insufficient absorption due to quaternary nature. It also failed to inhibit β-hematin formation in contrast to **270**, indicating its antiplasmodial activity is due to a different mechanism of action.

Ablordeppey et al. synthesized isosteres of **44**.[192] The carbon (indenoquinoline) and oxygen (benzofuroquinoline) isosteres were significantly less potent than the parent nitrogen (indoloquinolines) isostere, while the, benzothieno[3,2-*b*]pyridines like (**271**, IC_{50} = 0.18 μg/mL) obtained by removal of ring D and replacement of nitrogen with sulfur were equipotent to **44** with no cytotoxicity. Moreira et al. designed cryptolepine analogs like **272** by incorporating an alkyldiamino side-chain at C-11, aiming to increase accumulation in the parasite food vacuole.[193] The analogs had IC_{50} values ranged in 22 and 184 nM, with a selectivity ratio higher than 10. Febrifugine (**273**) is a quinazoline alkaloid isolated from *Dichroa febrifuga* Lour as the active component against *P. falciparum*. Strong liver toxicity has precluded the use of **273** as a potential clinical drug. Structure–activity relationship studies have demonstrated that the 4-quinazolinone moiety plays an essential role, while presence of a 1″-amino group and C-2′, C-3″ *O*-functionalities is crucial for antimalarial activity. Zhu et al. synthesized febrifugine analogs by introducing extra nitrogen atoms, one or two electron-withdrawing group(s) or a bulky group in the quinazolinone ring.[194] Overall, these compounds closely resembled febrifugine itself by possessing a planar aromatic ring, a 1″-amino group, and C-2′, C-3″O-functionality. Compound **274** with an extra nitrogen atom on the position 5 or 6 of the aromatic ring (IC_{50} = 1.2 nM) possessed antimalarial activity comparable to **273**, while compound **275** (IC_{50} = 0.33 nM) with difluoride attached to C-5 and C-6 was superior to febrifugine. These compounds were 100 times less toxic than febrifugine. Oshima et al. also reported antimalarial activity of a series of febrifugine derivatives bearing structural modifications at: (i) the quinazoline ring, (ii) the linker, or (iii) the piperidine ring.[195] Thienopyrimidine analog **276** exhibited potent antimalarial activity and a high therapeutic selectivity both in vitro and in vivo [EC_{50} = 0.00306 μg/mL (*P. falciparum* FCR-3), ED_{50} = 2.95 mg/kg, LD_{50} = 88 mg/kg (*P. berghei*)]. Recently, Bringmann et al. have synthesized a series of photoactive and fluorescent derivatives of naphthylisoquinoline alkaloids to identify their putative target.[196] The dansyl-functionalized dioncophylline A derivatives were good candidates for visualizing the in vitro distribution of these alkaloids. Barbaras et al. evaluated bis-cationic dimeric derivatives of nostocarboline (**64**) against *P. falciparum* K1.[56] For dimers long and flexible linkers were preferred and all semisynthetic analogs displayed IC_{50} < 100 nM. While, the effect of linker length on antiplasmodial activity of dimers was very small, its effect on cytotoxicity was more pronounced. Cytotoxicity increased with linker length leading to decreased selectivity for longer linkers. Compound **277** with five atom linkers displayed highest potency (IC_{50} = 18 nM) and an excellent selectivity of >2500-fold against the L6 cell line.

12.2. Semisynthetic artemisinin derivatives (Fig. 21)

Chinese researchers discovered antimalarial compound artemisinin **278a** (IC_{50} = 0.5 ng/mL), which is currently established as a clinically important drug against CQ resistant *P. falciparum.* The biological activity and the challenging structure of artemisinin have prompted extensive synthetic efforts to disclose more potent

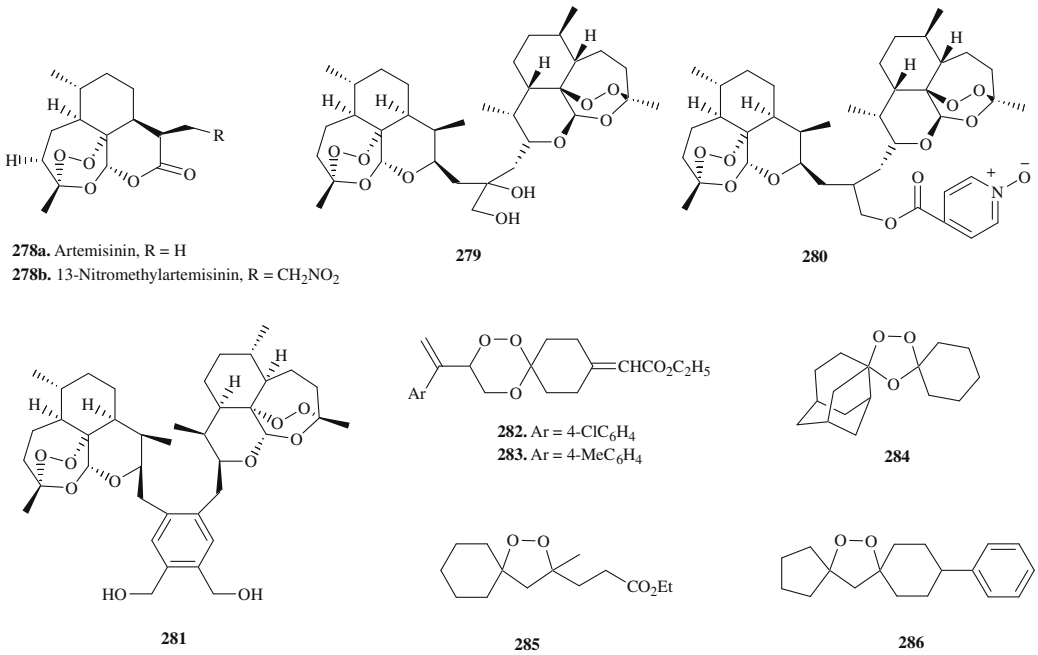


Figure 21. Semisynthetic artemisinin analogs.

analogs. Artemisinin analogs modified at C-3 and C-13 were prepared by Han et al. from artemisinic acid.[197] Artemisinic acid was modified through allylic oxidation at C-3 or conjugate addition at C-13 to afford methyl artemisinates, which upon photooxidation yielded artemisinin analogs. Among these analogs, 13-nitromethylartemisinin (**278b**) produced activity comparable to artemisinin (IC_{50} = 0.68 ng/mL). 13-(1-Nitroethyl)artemisinin was 20-fold less active, indicating that the activity was sensitive to the bulkiness of the side chain.

Posner et al. used naturally occurring trioxane artemisinin to synthesize its dimers. Alcohol, diol and ketone dimers were 10 times more potent than artemisinin. Most potent dimer **279** exhibited IC_{50} of 0.59 nM,[198] while isonicotinate N-oxide dimer **280** was more efficacious than clinically used sodium artesunate via both oral (ED_{50} = 2 mg/kg/day × 4) and intravenous (ED_{50} = 0.8 mg/kg/day × 4) administration.[199] Among the C-10 nonacetal trioxane dimers, the most active compound **281**, a benzyl alcohol dimer produced IC_{50} value of 0.77 nM.[200]

In this section we have also included advances made in the past three years in the synthetic trioxanes, trioxolanes and dioxolanes. Singh et al. reported novel functionalized 1,2,4-trioxanes such as **282** and **283**, which showed significant in vivo protection against multi-drug resistant *P. yoelii nigeriensis*.[201] Vennerstrom et al. identified spiro- and dispiro-1,2,4-trioxolanes as a new class of synthetic antimalarial peroxides and discovered **284** as a novel antimalarial lead.[202] Later, Vennerstrom et al. synthesized spiro- and dispiro-1,2-dioxolanes **285** and **286**. However, 1,2-dioxolanes were either inactive or less potent than the corresponding 1,2,4-trioxolanes or artemisinin. Based on this study, Vennerstrom et al. postulated that for optimal antimalarial potency, peroxide structures that permit rapid β-scission reactions (H shifts) to form primary or secondary carbon-centered radicals are preferred, rather than structures that undergo further reduction of the initially formed Fe(III) complexed oxy radicals.[203]

12.3. Miscellaneous semisynthetic antimalarials [Figs. 22 and 23]

Go et al. studied in vitro and in vivo antimalarial activities of ring B alkoxylated and ring B hydroxylated chalcones.[204] The most active compound **287** exhibited IC_{50} of 2 μM. Structure–activity relationships were also derived by applying the projections to latent structures (PLS) method. Brun et al. synthesized a series of aurones, tricyclic phenolic compounds characterized by the presence of a benzylidine function.[205] The most active compound **288** had IC_{50} values of 0.007 and 0.18 μM for K1 and NF54 strains, respectively. It was observed that aurones with hydroxyl and methoxy groups were more active than lipophilic aurones with no oxygen substituents. Antiplasmodial activity seemed to be influenced by the oxygenation pattern on the aromatic rings. Compounds bearing an oxygen substituent in the B-ring had better activity, while presence of bulky groups on A-ring reduced the activity. Kundu et al. used lupeol (**243**) a pentacyclic triterpene, as a scaffold for the synthesis of lupeol-based libraries.[206] Compounds like X4Y10 (**289**) containing suberic acid and 4-bromobenzyl alcohol moieties exhibited 7–9-fold increase in the biological activity in comparison to lupeol (MIC = 13.07 μM).

Hamann et al. performed microbial and chemical transformation studies of the marine sesquiterpene phenols isolated from the Jamaican sponge *Didiscus oxeata*.[207] From the metabolites obtained by preparative-scale fermentation of (*S*)-(+)-curcuphenol (**290**) with *Kluyveromyces marxianus*, (*S*)-(+)-15-hydroxycurcuphenol (**291**) displayed best antimalarial activity against D6 clone and W2 clone of *P. falciparum* (MIC = 3800 and 2900 ng/mL, respectively). Hagai et al. reported that aminoheptanoylated peptide NC7-P, based on K_4-S4(1-13), displayed improved antimalarial efficiency and reduced hemolysis. NC7-P dissipated the parasite plasma membrane potential and caused depletion of intraparasite potassium at non-hemolytic conditions.[208]

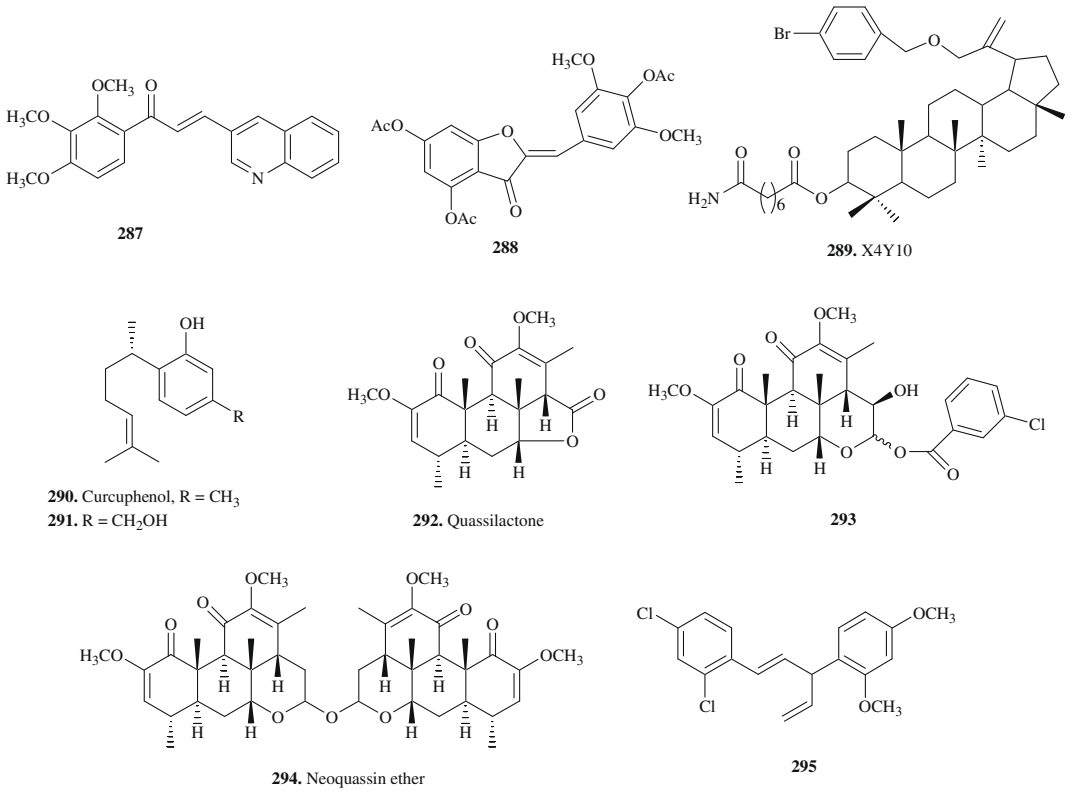


Figure 22. Miscellaneous semisynthetic antimalarials.

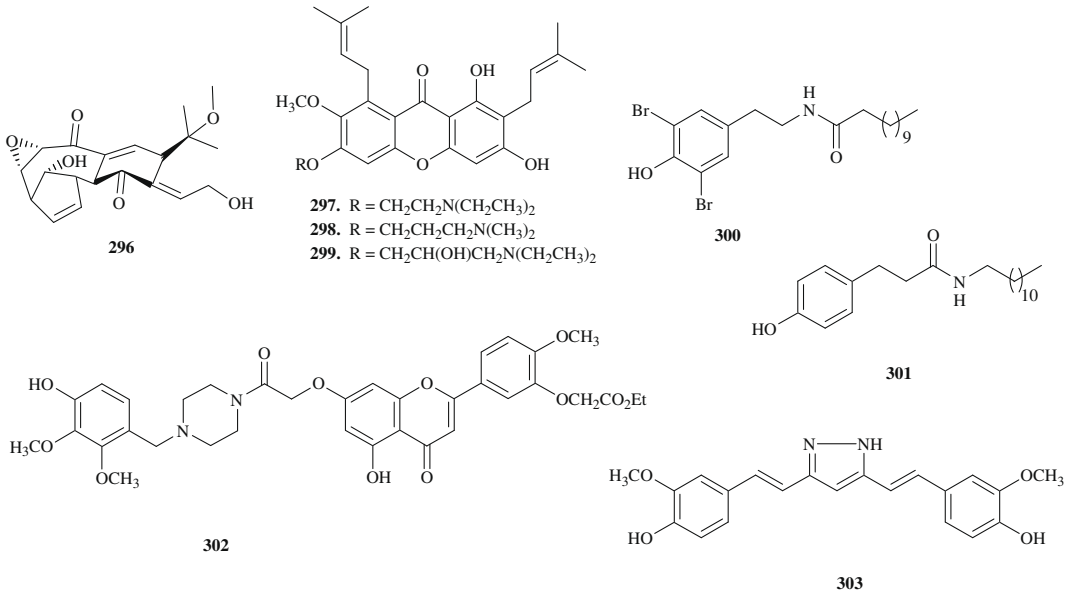


Figure 23. Miscellaneous semisynthetic antimalarials.

Lang'at-Thoruwa et al. converted quassin (**157**) chemically into the γ-lactone quassilactone (**292**) in their attempt to enhance antiplasmodial activity.[209] The activity of **292** was 40-fold greater than quassin, while intermediate **293** was 506-fold more active with a high selectivity index of 112 (IC_{50} = 23.0 and 1.80 μM, respectively). Neoquassin ether, a dimer (**294**), linked at C-16 possessed moderate antiplasmodial activity (IC_{50} = 9.70 μM). Christensen et al. used hinokiresinol, the *E*-isomer of nyasol as a template and synthesized a series of norneolignans by changing the substituents and side chain of hinokiresinol.[210] One of the analogs, **295** was about 10 times more potent than hinokiresinol (IC_{50} = 1.5 μg/mL). Clair while carrying out the total synthesis of terpenes, hexacyclinol, *epi*-5-hexacyclinol, and desoxohexacyclinol present in *Panus rudis*, found that some of the intermediates exhibit antimalarial activities.[211] The most active compound **296** displayed IC_{50} value of 2.1 ± 0.7 nM and ED_{50} of 5.2 mg/kg against chloroquine sensitive *P. berghei*.

Mangostin derivatives were tested in vitro against *P. falciparum* strain K1.[146] Synthetic derivatives of mangostin with methoxy group, acyl group and alkylcyano groups at one or both hydroxyl groups were less active (IC_{50} > 17.0 μM). Dihydroxypropyl group attached at 6-OH increased the activity (IC_{50} = 7.4 μM). The highest activity was observed with alkylamino groups (**297**–**299**, IC_{50} < 1.0 μM). Disruption of the prenyl side-chains of mangostin also led to marked reduction in activity (IC_{50} > 20 μM). It has been speculated that hydroxyxanthones like mangostin exert their antiplasmodial activity through formation of soluble complexes with heme, thereby inhibiting parasite hemozoin formation. The better activity of derivatives with alkylamino groups **297**–**299** can be accounted to the presence of protonable nitrogen atoms for ionic interaction with the heme propionate groups and increased accumulation in the malaria parasite food vacuole. Gutierrez et al. synthesized and evaluated the antiplasmodial activity of derivatives of tyramine.[168] The derivatives with a fatty acid moiety had activity very similar to those of natural analogs. Increase in the number of carbons of the fatty acid chain produced an increase in potency while the presence of polar groups on the fatty acid chain decreased the potency. The introduction of bromine atoms on the tyramine aromatic ring (**300**, IC_{50} = 17.0 μM) and change in the position of amide bond increased the antimalarial activity (**301**, IC_{50} = 8.0 μg/mL). Lewin et al. reported antiplasmodial activity of flavonoid derivatives containing a piperazinyl chain.[212] The compounds having a 2,3,4-trimethoxybenzylpiperazinyl chain attached to the flavone at the 7-phenol group were most active (e.g., **302**, IC_{50} = 0.6 μM). Surolia et al. synthesized di-*O*-methylcurcumin, isoxazole, and pyrazole derivatives of curcumin.[213] Pyrazole analog of curcumin **303** exhibited 7–9-fold higher antimalarial potency against CQ-S and CQ-R *P. falciparum* strains (IC_{50} of 0.48 and 0.45 μM, respectively).

13. Conclusions

Medicinal plants have provided valuable and clinically used antimalarials like quinine and artemisinin. In past few years, not only plants but fungi, bacteria and marine organisms have also been intensively investigated for obtaining new antimalarial agents. As discussed in this review, several compounds containing unique structural composition have been isolated and characterized from natural sources. These natural products have exhibited promising antimalarial activities in vitro and in vivo. However, limitations such as toxicity, low bioavailability and/or poor solubility have restricted the scope of use for several natural products in humans. Nevertheless, nature provides novel leads, which can be developed into safe drugs by synthetic strategies as exemplified by artemether, and quinoline class of antimalarials. Therefore, compounds described herein provide useful bioactive synthons, which could be modulated to obtain antimalarials active against not only drug-sensitive, but also drug-resistant and multi-drug resistant strains of *Plasmodium*. In this direction, semisynthetic approaches to newer and modified antimalarials have provided useful insights into their applicability in antimalarial drug discovery. To conclude, nature has been generous in providing several remedies for the treatment of disease like malaria. However, still there is vast unexplored flora and fauna, which when systematically explored will provide additional new leads and drugs for malaria chemotherapy.

References and notes

1. Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. *Nature* **2005**, *434*, 214.
2. Kumar, S.; Epstein, J. E.; Richie, T. L.; Nkrumah, F. K.; Soisson, L.; Carucci, D. J.; Hoffman, S. L. *Trends Parasitol.* **2002**, *18*, 129.

3. Sharma, J. D.; Sharma, P. *Phytother. Res.* **2001**, *15*, 1.
4. Fournet, A.; Muñoz, V. *Curr. Top. Med. Chem.* **2002**, *2*, 1215.
5. Go, M. L. *Med. Res. Rev.* **2003**, *23*, 456.
6. Saxena, S.; Pant, N.; Jain, D. C.; Bhakuni, R. S. *Curr. Sci.* **2003**, *85*, 1314.
7. Kapoor, V. K.; Kumar, K. *Prog. Med. Chem.* **2005**, *43*, 189.
8. Vangapandu, S.; Jain, M.; Kaur, K.; Patil, P.; Patel, S.; Jain, R. *Med. Res. Rev.* **2007**, *27*, 65.
9. Baelmans, R.; Deharo, E.; Bourdy, G.; Muñoz, V.; Quenevo, C.; Sauvain, M.; Ginsburg, H. *J. Ethnopharmacol.* **2000**, *73*, 271.
10. Marshall, S. J.; Russell, P. F.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Wright, C. W. *Phytother. Res.* **2000**, *14*, 356.
11. Antoun, M. D.; Ramos, Z.; Vazques, J.; Oquendo, I.; Proctor, G. R.; Gerena, L.; Franzblau, S. G. *Phytother. Res.* **2001**, *15*, 638.
12. Asres, K.; Bucar, F.; Knauder, E.; Yardley, V.; Kendrick, H.; Croft, S. L. *Phytother. Res.* **2001**, *15*, 613.
13. Beha, E.; Jung, A.; Wiesner, J.; Rimpler, H.; Lanzer, M.; Heinrich, M. *Phytother. Res.* **2004**, *18*, 236.
14. Brandäo, M. G. L.; Nery, C. G. C.; Mamäo, M. A. S.; Kretlli, A. U. *Phytochemistry* **1998**, *48*, 397.
15. Andrade-Neto, V. F.; Brandao, M. G. L.; Oliveira, F. Q.; Casali, V. W.; Njaine, B.; Zalis, M. G.; Oliveira, L. A.; Kretlli, A. U. *Phytother. Res.* **2004**, *18*, 634.
16. Rasoanaivo, P.; Ramanitrahasimbola, D.; Rafatro, H.; Rakotondramanana, D.; Robijaona, B.; Rakotozafy, A.; Ratsimamanga-Urverg, S.; Labaïed, M.; Grellier, P.; Allorge, L.; Mambu, L.; Frappier, F. *Phytother. Res.* **2004**, *18*, 742.
17. Tasdemir, D.; Brun, R.; Perozzo, R.; Dönmez, A. A. *Phytother. Res.* **2005**, *19*, 162.
18. Tchoumbougnang, E.; Zollo, P. H.; Dagne, E.; Mekonnen, Y. *Planta Med.* **2005**, *71*, 20.
19. Okokon, J. E.; Ita, B. N.; Udokpoh, A. E. *J. Ethnopharmacol.* **2006**, *107*, 175.
20. de Mesquita, M. L.; Grellier, P.; Mambu, L.; de Paula, J. E.; Espindola, L. S. *J. Ethnopharmacol.* **2007**, *110*, 165.
21. Nguyen-Pouplin, J.; Tran, H.; Tran, H.; Phan, T. A.; Dolecek, C.; Farrar, J.; Tran, T. H.; Caron, P.; Bodo, B.; Grellier, P. *J. Ethnopharmacol.* **2007**, *109*, 417.
22. Muthaura, C. N.; Rukunga, G. M.; Chhabra, S. C.; Mungai, G. M.; Njagi, E. N. M. *J. Ethnopharmacol.* **2007**, *114*, 377.
23. Garavito, G.; Rincón, J.; Arteaga, L.; Hata, Y.; Bourdy, G.; Gimenez, A.; Pinzón, R.; Deharo, E. *J. Ethnopharmacol.* **2006**, *107*, 460.
24. Muregi, F. W.; Ishih, A.; Suzuki, T.; Kino, H.; Amano, T.; Mkoji, G. M.; Miyase, T.; Terada, M. *Phytother. Res.* **2007**, *21*, 337.
25. Muthaura, C. N.; Rukunga, G. M.; Chhabra, S. C.; Omar, S. A.; Guantai, A. N.; Gathirwa, J. W.; Tolo, F. M.; Mwitari, P. G.; Keter, L. K.; Kirira, P. G.; Kimani, C. W.; Mungai, G. M.; Njagi, E. N. *Phytother. Res.* **2007**, *21*, 860.
26. Mendiola, J.; Hernández, H.; Sariego, I.; Rojas, L.; Otero, A.; Ramírez, A.; Chávez, M. A.; Payrol, J. A.; Hernández, A. *Trans. Royal Soc. Trop. Med. Hyg.* **2006**, *100*, 909.
27. Francois, G.; Timperman, G.; Eling, W.; Assi, L. A.; Holenz, J.; Bringmann, G. *Antimicrob. Agents Chemother.* **1997**, *41*, 2533.
28. Hallock, Y. F.; Manfredi, K. P.; Dai, J. R.; Cardellina, J. H., 2nd; Gulakowski, R. J.; McMahon, J. B.; Schäffer, M.; Stahl, M.; Gulden, K. P.; Bringmann, G.; Francois, G.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 677.
29. Hallock, Y. F.; Cardellina, J. H.; Schäffer, M.; Bringmann, G.; Francois, G.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1729.
30. Bringmann, G.; Günther, C.; Saeb, W.; Mies, J.; Wickramasinghe, A.; Mudogo, V.; Brun, R. *J. Nat. Prod.* **2000**, *63*, 1333.
31. Bringmann, G.; Hamm, A.; Günther, C.; Michel, M.; Brun, R.; Mudogo, V. *J. Nat. Prod.* **2000**, *63*, 1465.
32. Bringmann, G.; Messer, K.; Brun, R.; Mudogo, V. *J. Nat. Prod.* **2002**, *65*, 1096.
33. Bringmann, G.; Dreyer, M.; Faber, J. H.; Dalsgaard, P. W.; Staerk, D.; Jaroszewski, J. W.; Ndangalasi, H.; Mbago, F.; Brun, R.; Christensen, S. B. *J. Nat. Prod.* **2004**, *67*, 743.
34. Campbell, W. E.; Nair, J. J.; Gammon, D. W.; Bastida, J.; Codina, C.; Viladomat, F.; Smith, P. J.; Albrecht, C. F. *Planta Med.* **1998**, *64*, 91.
35. Sener, B.; Orhan, I.; Satayavivad, J. *Phytother. Res.* **2003**, *17*, 1220.
36. Angerhofer, C. K.; Guinaudeau, H.; Wongpanich, V.; Pezzuto, J. M.; Cordell, G. A. *J. Nat. Prod.* **1999**, *62*, 59.
37. Mambu, L.; Martin, M. T.; Razafimahefa, D.; Ramanitrahasimbola, D.; Rasoanaivo, P.; Frappier, F. *Planta Med.* **2000**, *66*, 537.
38. Roumy, V.; Fabre, N.; Souard, F.; Massou, S.; Bourdy, G.; Maurel, S.; Valentin, A.; Moulis, C. *Planta Med.* **2006**, *72*, 894.
39. Wright, C. W.; Marshall, S. J.; Russell, P. F.; Anderson, M. M.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Schiff, P. L. *J. Nat. Prod.* **2000**, *63*, 1638.
40. Lin, L. Z.; Hu, S. F.; Chu, M.; Chan, T. M.; Chai, H.; Angerhofer, C. K.; Pezzuto, J. M.; Cordell, G. A. *Phytochemistry* **1999**, *50*, 829.
41. Muhammad, I.; Dunbar, D. C.; Takamatsu, S.; Walker, L. A.; Clark, A. M. *J. Nat. Prod.* **2001**, *64*, 559.
42. Frédérich, M.; Tits, M.; Angenot, L. *Trans. Royal Soc. Trop. Med. Hyg.* **2008**, *102*, 11.
43. Frédérich, M.; Tits, M.; Hayette, M. P.; Brandt, V.; Penelle, J.; DeMol, P.; Llabrès, G.; Angenot, L. *J. Nat. Prod.* **1999**, *62*, 619.
44. Paulo, A.; Gomes, E. T.; Steele, J.; Warhurst, D. C.; Houghton, P. J. *Planta Med.* **2000**, *66*, 30.
45. Frédérich, M.; Hayette, M. P.; Tits, M.; DeMol, P.; Angenot, L. *Planta Med.* **2001**, *67*, 523.
46. Frédérich, M.; De Pauw, M. C.; Llabrès, G.; Tits, M.; Hayette, M. P.; Brandt, V.; Penelle, J.; DeMol, P.; Angenot, L. *Planta Med.* **2000**, *66*, 262.
47. Frédérich, M.; De Pauw, M. C.; Prosperi, C.; Tits, M.; Brandt, V.; Penelle, J.; Hayette, M. P.; DeMol, P.; Angenot, L. *J. Nat. Prod.* **2001**, *64*, 12.
48. Frédérich, M.; Jacquier, M. J.; Thépenier, P.; DeMol, P.; Tits, M.; Philippe, G.; Delaude, C.; Angenot, L.; Zèches-Hanrot, M. *J. Nat. Prod.* **2002**, *65*, 1381.
49. Philippe, G.; Prost, E.; Nuzillard, J. M.; Zèches-Hanrot, M.; Tits, M.; Angenot, L.; Frédérich, M. *Tetrahedron Lett.* **2002**, *43*, 3387.
50. Philippe, G.; Nguyen, L.; Angenot, L.; Frédérich, M.; Moonen, G.; Tits, M.; Rigo, J. M. *Eur. J. Pharmacol.* **2006**, *530*, 15.
51. Philippe, G.; DeMol, P.; Angenot, L.; Tits, M.; Frédérich, M. *Planta Med.* **2007**, *73*, 478.
52. Kuo, P. C.; Shi, L. S.; Damu, A. G.; Su, C. R.; Huang, C. H.; Ke, C. H.; Wu, J. B.; Lin, A. J.; Bastow, K. F.; Lee, K. H.; Wu, T. S. *J. Nat. Prod.* **2003**, *66*, 1324.
53. Fédérich, M.; Cristino, A.; Choi, Y. H.; Verpoorte, R.; Tits, M.; Angenot, L.; Prost, E.; Nuzillard, J. M.; Zèches-Honrot, M. *Planta Med.* **2004**, *70*, 72.
54. F de Andrade-Neto, V.; Pohlit, A. M.; Pinto, A. C. S.; Silva, E. C. C.; Nogueira, K. L.; Melo, M. R. S.; Henrique, M. C.; Amorim, R. C. N.; Silva, L. F. R.; Costa, M. R. F.; Nunomura, C. S. R.; Nunomura, S. M.; Alecrim, W. D.; Alecrim, M. G. C.; Chaves, F. C. M.; Vieira, P. P. R. *Mem. Inst. Oswaldo Cruz. Rio de Janeiro* **2007**, *102*, 359.
55. Sun, J.; Lou, H.; Dai, S.; Xu, H.; Zhao, F.; Liu, K. *Phytochemistry* **2008**, *69*, 1405.
56. Barbaras, D.; Kaiser, M.; Brun, R.; Gademann, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4413.
57. El Sayed, K. A.; Kelly, M.; Kara, U. A.; Ang, K. K.; Katsuyama, I.; Dunbar, D. C.; Khan, A. A.; Hamann, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 1804.
58. Rao, K. V.; Donia, M. S.; Peng, J.; Gracia-Palomero, E.; Alonso, D.; Martinez, A.; Medina, M.; Franzblau, S. G.; Tekwani, B. L.; Khan, S. I.; Wahyuono, S.; Willett, K. L.; Hamann, M. T. *J. Nat. Prod.* **2006**, *69*, 1034.
59. Federici, E.; Palazzino, G.; Nicoletti, M.; Galeffi, C. *Planta Med.* **2000**, *66*, 93.
60. Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067.
61. Lazaro, J. E.; Nitcheu, J.; Predicala, R. Z.; Mangalindan, G. C.; Nesslany, F.; Marzin, D.; Concepcion, G. P.; Diquet, B. *J. Nat. Toxins.* **2002**, *11*, 367.
62. Ovenden, S. P. B.; Cao, S.; Leong, C.; Flotow, H.; Gupta, M. P.; Buss, A. D.; Butler, M. S. *Phytochemistry* **2002**, *60*, 175.
63. Chea, A.; Hout, S.; Buna, S. S.; Tabatadze, N.; Gasquet, M.; Azas, N.; Elias, R.; Balansard, G. *J. Ethnopharmacol.* **2007**, *112*, 132.
64. Waffo, A. F.; Coombes, P. H.; Crouch, N. R.; Mulholland, D. A.; El Amin, S. M. M.; Smith, P. J. *Phytochemistry* **2007**, *68*, 663.
65. Benoit-Vical, F.; Saléry, M.; Soh, P. N.; Ahond, A.; Poupat, C. *Planta Med.* **2008**, *74*, 438.
66. Carraz, M.; Jossang, A.; Rasoanaivo, P.; Mazier, D.; Frappier, F. *Bioorg. Med. Chem.* **2008**, *16*, 6186.
67. Rumalla, C. S.; Jadhav, A. N.; Smillie, T.; Fronczek, F. R.; Khan, I. A. *Phytochemistry* **2008**, *69*, 1756.
68. Francois, G.; Passreiter, C. M.; Woerdenbag, H. J.; Van Looveren, M. *Planta Med.* **1996**, *62*, 126.
69. Isaka, M.; Jaturapat, A.; Kladwang, W.; Punya, J.; Lertwerawat, Y.; Tanticharoen, M.; Thebtaranonth, Y. *Planta Med.* **2000**, *66*, 473.
70. Goffin, E.; Ziemons, E.; DeMol, P.; DeMadureira Mao, C.; Martins, A. P.; da Cunha, A. P.; Philippe, G.; Tits, M.; Angenot, L.; Fédérich, M. *Planta Med.* **2002**, *68*, 543.
71. Osterhage, C.; König, G. M.; Höller, U.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 306.
72. Topcu, G.; Aydogmus, Z.; Imre, S.; Gören, A. C.; Pezzuto, J. M.; Clement, J. A.; Kingston, D. G. *J. Nat. Prod.* **2003**, *66*, 1505.
73. Kraft, C.; Jennet-Siems, K.; Siems, K.; Jakupovic, J.; Mavi, S.; Bienzle, U.; Eich, E. *Phytother. Res.* **2003**, *17*, 123.
74. Francois, G.; Passreiter, C. M. *Phytother. Res.* **2004**, *18*, 184.
75. Prakash Chaturvedula, V. S.; Farooq, A.; Schilling, J. K.; Malone, S.; Derveld, I.; Werkhoven, M. C. M.; Wisse, J. H.; Ratsimbason, M.; Kingston, D. G. I. *J. Nat. Prod.* **2004**, *67*, 2053.
76. Grazón, S. P.; Rodríguez, A. D.; Sánchez, J. A.; Ortega-Barria, E. *J. Nat. Prod.* **2005**, *68*, 1354.
77. Vongvanich, N.; Kittakoop, P.; Charoenchai, P.; Intamas, S.; Sriklung, K.; Thebtaranonth, Y. *Planta Med.* **2006**, *72*, 1427.
78. Karioti, A.; Skaltsa, H.; Zhang, X.; Tonge, P. J.; Perozzo, R.; Kaiser, M.; Franzblau, G. S.; Tasdemir, D. *Phytomedicine* **2008**, *15*, 1125.
79. Traore, F.; Faure, R.; Ollivier, E.; Gasquet, M.; Azas, N.; Debrauwer, L.; Keita, A.; Timon-David, P.; Balansard, G. *Planta Med.* **2000**, *66*, 368.
80. Camacho, M. R.; Mata, R.; Castaneda, P.; Kirby, G. C.; Warhurst, D. C.; Croft, S. L.; Phillipson, J. D. *Planta Med.* **2000**, *66*, 463.
81. Benoit-Vical, F.; Imbert, C.; Bonfils, J. P.; Sauvaire, Y. *Phytochemistry* **2003**, *62*, 747.
82. Thiem, D. A.; Sneden, A. T.; Khan, S. I.; Tekwani, B. L. *J. Nat. Prod.* **2005**, *68*, 251.
83. Saewan, N.; Sutherland, J. D.; Chantrapromma, K. *Phytochemistry* **2006**, *67*, 2288.
84. Sawadjoon, S.; Kittakoop, P.; Isaka, M.; Kirtikara, K.; Madla, S.; Thebtaranonth, Y. *Planta Med.* **2004**, *70*, 1085.
85. Ma, C.; Zhang, H. J.; Tan, G. T.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Fong, H. H. S. *J. Nat. Prod.* **2006**, *69*, 346.
86. Murata, T.; Miyase, T.; Muregi, F. W.; Naoshima-Ishibashi, Y.; Umehara, K.; Warashina, T.; Kanou, S.; Mkoji, G. M.; Terada, M.; Ishih, A. *J. Nat. Prod.* **2008**, *71*, 167.
87. Wright, A. D.; Wang, H.; Gurrath, M.; König, G. M.; Kocak, G.; Neumann, G.; Loria, P.; Foley, M.; Tilley, L. *J. Med. Chem.* **2001**, *44*, 873.
88. Uys, A. C. U.; Malan, S. F.; van Dyk, S.; van Zyl, R. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2167.
89. Sairafianpour, M.; Christensen, J.; Staerk, D.; Budnik, B. A.; Kharazmi, A.; Bagherzadeh, K.; Jaroszewski, J. W. *J. Nat. Prod.* **2001**, *64*, 1398.

90. Riel, M. A.; Kyle, D. E.; Milhous, W. K. *J. Nat. Prod.* **2002**, *65*, 614.
91. Clarkson, C.; Campbell, W. E.; Smith, P. *Planta Med.* **2003**, *69*, 720.
92. Ziegler, H. L.; Jensen, T. H.; Christensen, J.; Staerk, D.; Hägerstrand, H.; Sittie, A. A.; Olsen, C. E.; Staalsø, T.; Ekpe, P.; Jaroszewski, J. W. *Planta Med.* **2002**, *68*, 547.
93. Asili, J.; Lambert, M.; Ziegler, H. L.; Staerk, D.; Sairafianpour, M.; Witt, M.; Asghari, G.; Ibrahimi, I. S.; Jaroszewski, J. W. *J. Nat. Prod.* **2004**, *67*, 631.
94. Ospina, C. A.; Rodríguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357.
95. Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661.
96. Wei, X.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; González, J. *Tetrahedron* **2004**, *60*, 11813.
97. Ospina, C. A.; Rodríguez, A. D.; Sánchez, J. A.; Barria-Ortega, E.; Capson, T. L.; Mayer, A. M. S. *J. Nat. Prod.* **2005**, *68*, 1519.
98. Kenmogne, M.; Prost, E.; Harakat, D.; Jacquier, M. J.; Frédérich, M.; Sondengam, L. B.; Zèches, M.; Waffo-Téguo, P. *Phytochemistry* **2006**, *67*, 433.
99. Mambu, L.; Philippe, G.; Florent, L.; Joyeau, R.; Ramanitrahasimbola, D.; Rasoanaivo, P.; Frappier, F. *Phytochemistry* **2006**, *67*, 444.
100. Mongkolvisut, W.; Sutthivaiyakit, S. *J. Nat. Prod.* **2007**, *70*, 1434.
101. Chinworrungsee, M.; Kittakoop, P.; Isaka, M.; Rungrod, A.; Tanticharoen, M.; Thebtaranonth, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1965.
102. Moein, M. R.; Pawar, R. S.; Khan, S. I.; Tekwani, B. L.; Khan, I. A. *Phytother. Res.* **2008**, *22*, 283.
103. Okunade, A. L.; Bikoff, R. E.; Casper, S. J.; Oksman, A.; Goldberg, D. E.; Lewis, W. H. *Phytother. Res.* **2003**, *17*, 675.
104. Kuo, P. C.; Damu, A. G.; Lee, K. H.; Wu, T. S. *Bioorg. Med. Chem.* **2004**, *12*, 537.
105. Chan, K. L.; Choo, C. Y.; Abdullah, N. R.; Ismail, Z. *J. Ethnopharmacol.* **2004**, *92*, 223.
106. Muhammad, I.; Bedir, E.; Khan, S. I.; Tekwni, B. L.; Khan, I. A.; Takamatsu, S.; Pelletier, J.; Walker, L. A. *J. Nat. Prod.* **2004**, *67*, 772.
107. Wright, C. W. *J. Ethnopharmacol.* **2005**, *100*, 67.
108. Elford, B. C. *Parasitol. Today* **1986**, *2*, 309.
109. Chanphen, R.; Thebtaranonth, Y.; Wanauppathamkul, S.; Yuthavong, Y. *J. Nat. Prod.* **1998**, *61*, 1146.
110. Jenett-Siems, K.; Siems, K.; Jakupovic, J.; Solis, P. N.; Gupta, M. P.; Mockenhaupt, F. P.; Bienzle, U.; Eich, E. *Planta Med.* **2000**, *66*, 384.
111. Bringmann, G.; Ochse, M.; Zotz, G.; Peters, K.; Peters, E. M.; Brun, R.; Schlauer, J. *Phytochemistry* **2000**, *53*, 965.
112. Kraft, C.; Jenett-Siems, K.; Siems, K.; Gupta, M. P.; Bienzle, U.; Eich, E. *J. Ethnopharmacol.* **2000**, *73*, 131.
113. Limmatvapirat, C.; Sirisopanaporn, S.; Kittakoop, P. *Planta Med.* **2004**, *70*, 276.
114. Torres-Mendoza, D.; Gongález, J.; Ortega-Barria, E.; Heller, M. V.; Capson, T. L.; McPhail, K.; Gerwick, W. H.; Cubilla-Rios, L. *J. Nat. Prod.* **2006**, *69*, 826.
115. Kirmizibekmez, H.; Calis, I.; Perozzo, R.; Brun, R.; Dönmez, A. A.; Linden, A.; Rüedi, P.; Tasdemir, D. *Planta Med.* **2004**, *70*, 711.
116. Tasdemir, D.; Güner, N. D.; Perozzo, R.; Brun, R.; Dönmez, A. A.; Calis, I.; Rüedi, P. *Phytochemistry* **2005**, *66*, 355.
117. Nunome, S.; Ishiyama, A.; Kobayashi, M.; Otoguro, K.; Kiyohara, H.; Yamada, H.; Omura, S. *Planta Med.* **2004**, *70*, 76.
118. Ichino, C.; Kiyohara, H.; Soonthornchareonnon, N.; Chuakul, W.; Ishiyama, A.; Sekiguchi, H.; Namatame, M.; Otoguro, K.; Omura, S.; Yamada, H. *Planta Med.* **2006**, *72*, 611.
119. Mbwambo, Z. H.; Kapingu, M. C.; Moshi, M. J.; Machumi, F.; Apers, S.; Cos, P.; Ferreria, D.; Marais, J. P.; Vanden Berghe, D.; Maes, L.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2006**, *69*, 369.
120. Sharma, S. K.; Parasuraman, P.; Kumar, G.; Surolia, N.; Surolia, A. *J. Med. Chem.* **2007**, *50*, 765.
121. Rochanakij, S.; Thebtaranonth, Y.; Yenjai, C.; Yuthavong, Y. *Southeast Asian J. Trop. Med. Public Health* **1985**, *16*, 66.
122. MacKinnon, S.; Durst, T.; Arnason, J. T.; Angerhofer, C.; Pezzuto, J.; Sanchez-Vindas, P. E.; Poveda, L. J.; Gbeassor, M. *J. Nat. Prod.* **1997**, *60*, 336.
123. Bray, D. H.; Warhurst, D. C.; Connolly, J. D.; O'Neill, M. J.; Phillipson, J. D. *Phytother. Res.* **1990**, *4*, 29.
124. Khalid, S. A.; Friedrichsen, G. M.; Kharazmi, A.; Theander, G. T.; Olsen, C. E.; Brøgger Christensen, S. *Phytochemistry* **1998**, *49*, 1769.
125. Bickii, J. N.; Njifutie, J.; Foyere, J. A.; Basco, L. K.; Ringwald, P. *J. Ethnopharmacol.* **2000**, *69*, 27.
126. Krief, B.; Martin, M. T.; Grellier, P.; Kasenene, J.; Sévenet, T. *Antimicrob. Agents Chemother.* **2004**, *48*, 3196.
127. Hay, A. E.; Ioset, J. R.; Ahua, K. M.; Diallo, D.; Brun, R.; Hostettmann, K. *J. Nat. Prod.* **2007**, *70*, 9.
128. Chen, M.; Theander, T. G.; Christensen, B. S.; Hviid, L.; Zhai, L.; Kharazmi, A. *Antimicrob. Agents Chemother.* **1994**, *38*, 1470.
129. Oketch-Rabah, H. A.; Dossaji, S. F.; Christensen, S. B.; Frydenvang, K.; Lemmich, E.; Cornett, C.; Olsen, C. E.; Chen, M.; Kharazmi, A.; Theander, T. *J. Nat. Prod.* **1997**, *60*, 1017.
130. Ducker-Eshun, G.; Jaroszewski, J. W.; Asomaning, W. A.; Oppong-Boachie, F.; Brøgger Christensen, S. *Phytother. Res.* **2004**, *18*, 128.
131. Yenesew, A.; Induli, M.; Derese, S.; Midiwo, J. O.; Heydenreich, M.; Peter, M. G.; Akala, H.; Wangui, J.; Liyala, P.; Waters, N. C. *Phytochemistry* **2004**, *65*, 3029.
132. Portet, B.; Fabre, N.; Roumy, V.; Gornitzka, H.; Bourdy, G.; Chevalley, S.; Sauvain, M.; Valentin, A.; Moulis, C. *Phytochemistry* **2007**, *68*, 1312.
133. Ngameni, B.; Watchueng, J.; Boyom, F. F.; Keumedjio, F.; Ngadjui, B. T.; Gut, T. J.; Abegaz, B. M.; Rosenthal, P. J. *Arkivoc* **2007**, 116.
134. Darkin-Rattray, S. J.; Gurnett, A. M.; Myers, R. W.; Dulski, P. M.; Crumley, T. M.; Allocco, J. J.; Cannova, C.; Meinke, P. T.; Colletti, S. L.; Bednarek, M. A.; Singh, S. B.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Schmatz, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 13143.
135. Gosh, J. K.; Shaool, D.; Guillaud, P.; Cicéron, L.; Mazier, D.; Kustanovich, I.; Shai, Y.; Mor, A. *J. Biol. Chem.* **1997**, *272*, 31609.
136. Nilanonta, C.; Isaka, M.; Kittakoop, P.; Palittapongarnpim, P.; Kamchonwongpaisan, S.; Pittayakhajonwut, D.; Tanticharoen, M.; Thebtaranonth, Y. *Planta Med.* **2000**, *66*, 756.
137. Mizuno, Y.; Makioka, A.; Kawazu, S.; Kano, S.; Kawai, S.; Akaki, M.; Aikawa, M.; Ohtomo, H. *Parasitol. Res.* **2002**, *88*, 844.
138. Fennell, B. J.; Carolan, S.; Pettit, G. R.; Bell, A. *J. Antimicrob. Chemother.* **2003**, *51*, 833.
139. Charoenvit, Y.; Brice, G. T.; Bacon, D.; Majam, V.; Williams, J.; Abot, E.; Ganeshan, H.; Sedegah, M.; Doolan, D. L.; Carucci, D. J.; Zimmerman, D. H. *Antimicrob. Agents Chemother.* **2004**, *48*, 2455.
140. Thongtan, J.; Saenboonrueng, J.; Rachtawee, P.; Isaka, M. *J. Nat. Prod.* **2006**, *69*, 713.
141. Linington, R. G.; Gonzalez, J.; Ureña, L. D.; Romero, L. I.; Ortega-Barría, E.; Gerwick, W. H. *J. Nat. Prod.* **2007**, *70*, 397.
142. McPhail, K. L.; Correa, J.; Linington, R. G.; Gonzalez, J.; Ortega-Barría, E.; Capson, T. L.; Gerwick, W. H. *J. Nat. Prod.* **2007**, *70*, 984.
143. Sabareesh, V.; Ranganayaki, R. S.; Raghothama, S.; Bopanna, M. P.; Balaram, H.; Srinivasan, M. C.; Balaram, P. *J. Nat. Prod.* **2007**, *70*, 715.
144. Likhitwitayawuid, K.; Phadungcharoen, T.; Krungkrai, J. *Planta Med.* **1998**, *64*, 70.
145. Hay, A. E.; Hélesbeux, J. J.; Duval, O.; Labaïed, M.; Grellier, P.; Richomme, P. *Life Sci.* **2004**, *75*, 3077.
146. Mahabusarakam, W.; Kuaha, K.; Wilairat, P.; Taylor, W. C. *Planta Med.* **2006**, *72*, 912.
147. Figueiredo, J. N.; Räz, B.; Séquin, U. *J. Nat. Prod.* **1998**, *61*, 718.
148. Weiss, C. R.; Moideen, S. V. K.; Croft, S. L.; Houghton, P. J. *J. Nat. Prod.* **2000**, *63*, 1306.
149. Likhitwitayawuid, K.; Kaewamatawong, R.; Ruangrungsi, N.; Krungkrai, J. *Planta Med.* **1998**, *64*, 237.
150. Abegaz, B. M.; Bezabih, M.; Msuta, T.; Brun, R.; Menche, D.; Mühlbacher, J.; Bringmann, G. *J. Nat. Prod.* **2002**, *65*, 1117.
151. Eyong, K. O.; Folefoc, G. N.; Kuete, V.; Beng, V. P.; Krohn, K.; Hussain, H.; Nkengfack, A. E.; Saeftel, M.; Sarite, S. R.; Hoerauf, A. *Phytochemistry* **2006**, *67*, 605.
152. Tansuwan, S.; Pornpakakul, S.; Roengsumran, S.; Petsom, A.; Muangsin, N.; Sihanonta, P.; Chaichit, N. *J. Nat. Prod.* **2007**, *70*, 1620.
153. Laurent, D.; Jullian, V.; Parenty, A.; Knibiehler, M.; Dorin, D.; Schmitt, S.; Lozach, O.; Lebouvier, N.; Frostin, M.; Alby, F.; Maurel, S.; Doerig, C.; Meijer, L.; Sauvain, M. *Bioorg. Med. Chem.* **2006**, *14*, 4477.
154. Oketch-Rabah, H. A.; Lemmich, E.; Dossaji, S. F.; Theander, T. G.; Olsen, C. E.; Cornett, C.; Kharazmi, A.; Christensen, S. B. *J. Nat. Prod.* **1997**, *60*, 458.
155. Yenjai, C.; Sripontan, S.; Sriprajun, P.; Kittakoop, P.; Jintasirikul, A.; Tanticharoen, M.; Thebtaranonth, Y. *Planta Med.* **2000**, *66*, 277.
156. Köhler, I.; Jenett-Siems, K.; Mockenhaupt, F. P.; Siems, K.; Jakupovic, J.; González, J. C.; Hernández, M. A.; Ibarra, R. A.; Berendsohn, W. G.; Bienzle, U.; Eich, E. *Planta Med.* **2001**, *67*, 89.
157. Argotte-Ramos, R.; Ramírez-Avila, G.; Rodríguez-Gutiérrez Mdel, C.; Olliva-Muñoz, M.; Lanz-Mendoza, H.; Rodríguez, M. H.; Gonzalez-Cortazar, M.; Alvarez, L. *J. Nat. Prod.* **2006**, *69*, 1442.
158. Moretti, C.; Sauvain, M.; Lavaud, C.; Massiot, G.; Bravo, J.; Muñoz, V. *J. Nat. Prod.* **1998**, *61*, 1390.
159. Kittakoop, P.; Kirtikara, K.; Tanticharoen, M.; Thebtaranonth, Y. *Phytochemistry* **2000**, *55*, 349.
160. Gochfeld, D. J.; Hamann, M. T. *J. Nat. Prod.* **2001**, *64*, 1477.
161. del Sol Jiménez, M.; Garzón, S. P.; Rodríguez, A. D. *J. Nat. Prod.* **2003**, *66*, 655.
162. Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 1561.
163. Jensen, J. F.; Kvist, L. P.; Brøgger Christensen, S. *J. Nat. Prod.* **2002**, *65*, 1915.
164. Gertsch, J.; Tobler, R. T.; Brun, R.; Sticher, O.; Heilmann, J. *Planta Med.* **2003**, *69*, 420.
165. Verotta, L.; Dell'Agli, M.; Giolito, A.; Guerrini, M.; Cabalion, P.; Bosisio, E. *J. Nat. Prod.* **2001**, *64*, 603.
166. Hernández-Medel Mdel, R.; Pereda-Miranda, R. *Planta Med.* **2002**, *68*, 556.
167. Subeki, S.; Matsuura, H.; Takahashi, K.; Yamasaki, M.; Yamato, O.; Maede, Y.; Katakura, K.; Kobayashi, S.; Trimurningsih, T.; Chairul, C.; Yoshihara, T. *J. Nat. Prod.* **2005**, *68*, 537.
168. Gutiérrez, M.; Capson, T. L.; Guzmán, H. M.; González, J.; Ortega-Barría, E.; Quinoá, E.; Riguera, R. *J. Nat. Prod.* **2006**, *69*, 1379.
169. Maskey, R. P.; Helmke, E.; Kayser, O.; Fiebig, H. H.; Maier, A.; Busche, A.; Laatsch, H. *J. Antibiot. (Tokyo)* **2004**, *57*, 771.
170. Abdel-Sattar, E.; Harraz, F. M.; Al-ansari, S. M.; El-Mekkawy, S.; Ichino, C.; Kiyohara, H.; Ishiyama, A.; Otoguro, K.; Omura, S.; Yamada, H. *Phytochemistry* **2008**, *69*, 2180.
171. Beldjoudi, N.; Mambu, L.; Labaïed, M.; Grellier, P.; Ramanitrahasimbola, D.; Rasoanaivo, P.; Martin, M. T.; Frappier, F. *J. Nat. Prod.* **2003**, *66*, 1447.
172. Ross, S. A.; Sultana, G. N. N.; Burandt, C. L.; ElSohly, M. A.; Marais, J. P. J.; Ferreira, D. *J. Nat. Prod.* **2004**, *67*, 88.
173. Saliba, K. J.; Ferru, I.; Kirk, K. *Antimicrob. Agents Chemother.* **2005**, *49*, 632.
174. Wright, A. D.; Lang-Unnasch, N. *Planta Med.* **2005**, *71*, 964.

175. Fotie, J.; Bohle, D. S.; Leimanis, M. L.; Georges, E.; Rukunga, G.; Nkengfack, A. E. *J. Nat. Prod.* **2006**, *69*, 62.
176. Londoño, B.; Arango, E.; Zapata, C.; Herrera, S.; Saez, J.; Blair, S.; Carmona-Fonseca, J. *Phytother. Res.* **2006**, *20*, 267.
177. Coppi, A.; Cabinian, M.; Mirelman, D.; Sinnis, P. *Antimicrob. Agents Chemother.* **2006**, *50*, 1731.
178. Rasmussen, H. B.; Brøgger Christensen, S.; Kvist, L. P.; Karazmi, A. *Planta Med.* **2000**, *66*, 396.
179. Nandakumar, D. N.; Nagaraj, V. A.; Vathsala, P. G.; Rangarajan, P.; Padmanaban, G. *Antimicrob. Agents Chemother.* **2006**, *50*, 1859.
180. Cui, L.; Miao, J.; Cui, L. *Antimicrob. Agents Chemother.* **2007**, *51*, 488.
181. Ramanandraibe, V.; Grellier, P.; Martin, M. T.; Deville, A.; Joyeau, R.; Ramanitrahasimbola, D.; Mouray, E.; Rasoanaivo, P.; Mambu, L. *Planta Med.* **2008**, *74*, 417.
182. Bunyapaiboonsri, T.; Yoiprommarat, S.; Khonsanit, A.; Komwijit, S. *J. Nat. Prod.* **2008**, *71*, 891.
183. Senn, M.; Gunzenhauser, S.; Brun, R.; Séquin, U. *J. Nat. Prod.* **2007**, *70*, 1565.
184. Pillay, P.; Vleggaar, R.; Maharaj, V. J.; Smith, P. J.; Lategan, C. A.; Choutaeu, F.; Chibale, K. *Phytochemistry* **2007**, *68*, 1200.
185. Chemaly, S. M.; Chen, C. T.; van Zyl, R. L. *J. Inorg. Biochem.* **2007**, *101*, 764.
186. Bajsa, J.; Singh, K.; Nanayakkara, D.; Duke, S. O.; Rimando, A. M.; Evidente, A.; Tekwani, B. L. *Biol. Pharm. Bull.* **2007**, *30*, 1740.
187. Na, M.; Meujo, D. A. F.; Kevin, D.; Hamann, M. T.; Anderson, M.; Hill, R. T. *Tetrahedron Lett.* **2008**, *49*, 6282.
188. Bringmann, G.; Ledermann, A.; Holenz, J.; Kao, M. T.; Busse, U.; Wu, H. G.; François, G. *Planta Med.* **1998**, *64*, 54.
189. Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Gökçek, Y.; Kendrick, H.; Phillips, R. M.; Pollet, P. L. *J. Med. Chem.* **2001**, *44*, 3187.
190. Jonckers, T. H. M.; van Miert, S.; Cimanga, K.; Bailly, C.; Colson, P.; De Pauw-Gillet, M. C.; van den Heuvel, H.; Claeys, M.; Lemière, F.; Esmans, E. L.; Rozenski, J.; Quirijnen, L.; Maes, L.; Dommisse, R.; Lemière, G. L.; Vlietinck, A.; Pieter, L. *J. Med. Chem.* **2002**, *45*, 3497.
191. Van Miert, S.; Hostyn, S.; Maes, B. U. W.; Cimanga, K.; Brun, R.; Kaiser, M.; Mátyus, P.; Dommisse, R.; Lemière, G.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2005**, *68*, 674.
192. Zhu, X. Y.; Mardenborough, L. G.; Li, S.; Khan, A.; Zhang, W.; Fan, P.; Jacob, M.; Khan, S.; Walker, L.; Ablordeppey, S. Y. *Bioorg. Med. Chem.* **2007**, *15*, 686.
193. Lavrado, J.; Paulo, A.; Gut, J.; Rosenthal, P. J.; Moreira, R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1378.
194. Zhu, S.; Meng, L.; Zhang, Q.; Wei, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1854.
195. Kikuchi, H.; Yamamoto, K.; Horoiwa, S.; Hirai, S.; Kasahara, R.; Hariguchi, N.; Matsumoto, M.; Oshima, Y. *J. Med. Chem.* **2006**, *49*, 4698.
196. Bringmann, G.; Gampe, C. M.; Reichert, Y.; Bruhn, T.; Faber, J. H.; Mikyna, M.; Reichert, M.; Leippe, M.; Brun, R.; Gelhaus, C. *J. Med. Chem.* **2007**, *50*, 6104.
197. Han, J.; Lee, J. G.; Min, S. S.; Park, S. H.; Angerhofer, C. K.; Cordell, G. A.; Kim, S. U. *J. Nat. Prod.* **2001**, *64*, 1201.
198. Posner, G. H.; Paik, I. H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2003**, *46*, 1060.
199. Posner, G. H.; McRiner, A. J.; Paik, I. H.; Sur, S.; Borstnik, K.; Xie, S.; Shapiro, T. A.; Alagbala, A.; Foster, B. *J. Med. Chem.* **2004**, *47*, 1299.
200. Paik, I. H.; Xie, S.; Shapiro, T. A.; Labonte, T.; Sarjeant, A. A. N.; Baege, A. C.; Posner, G. H. *J. Med. Chem.* **2006**, *49*, 2731.
201. Singh, C.; Malik, H.; Puri, S. K. *J. Med. Chem.* **2006**, *49*, 2794.
202. Dong, Y.; Chollet, J.; Matile, H.; Charman, S. A.; Chiu, F. C. K.; Charman, W. N.; Scorneaux, B.; Urwyler, H.; Tomas, J. S.; Scheurer, C.; Snyder, C.; Dorn, A.; Wang, X.; Karle, J. M.; Tang, Y.; Wittlin, S.; Brun, R.; Vennerstrom, J. L. *J. Med. Chem.* **2005**, *48*, 4953.
203. Wang, X.; Dong, Y.; Wittlin, S.; Creek, D.; Chollet, J.; Charman, S. A.; Tomas, J. S.; Scheurer, C.; Snyder, C.; Vennerstrom, J. L. *J. Med. Chem.* **2007**, *50*, 5840.
204. Liu, M.; Wilairat, P.; Go, M. L. *J. Med. Chem.* **2001**, *44*, 4443.
205. Kayser, O.; Kiderlen, A. F.; Brun, R. *Planta Med.* **2001**, *67*, 718.
206. Srinivasan, T.; Srivastava, G. K.; Pathak, A.; Batra, S.; Raj, K.; Singh, K.; Puri, S. K.; Kundu, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2803.
207. ElSayed, K. A.; Yousaf, M.; Hamann, M. T.; Avery, M. A.; Kelly, M.; Wipf, P. *J. Nat. Prod.* **2002**, *65*, 1547.
208. Efron, L.; Dagan, A.; Gaidukov, L.; Ginsburg, H.; Mor, A. *J. Biol. Chem.* **2002**, *277*, 24067.
209. Lang'at-Thoruwa, C.; Kirby, G. C.; Phillipson, J. D.; Warhurst, D. C.; Watt, R. A.; Wright, C. W. *J. Nat. Prod.* **2003**, *66*, 1486.
210. Skytte, D. M.; Nielsen, S. F.; Chen, M.; Zhai, L.; Olsen, C. E.; Brøgger Christensen, S. *J. Med. Chem.* **2006**, *49*, 436.
211. La Clair, J. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2769.
212. Auffret, G.; Labaied, M.; Frappier, F.; Rasoanaivo, P.; Grellier, P.; Lewin, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 959.
213. Mishra, S.; Karmodiya, K.; Surolia, N.; Surolia, A. *Bioorg. Med. Chem.* **2008**, *16*, 2894.

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