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Review

# Antimalarial compounds isolated from plants used in traditional medicine

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## Abstract

**Objectives** This review covers the compounds with antiplasmodial activity isolated from plants published from 2005 to the end of 2008, organized according to their phytochemical classes. Details are given for substances with IC50 values ≤ 11 $\mu$M.

**Key findings** Malaria is a major parasitic disease in many tropical and subtropical regions and is responsible for more than 1 million deaths each year in Africa. The rapid spread of resistance encourages the search for new active compounds. Nature and particularly plants used in traditional medicine are a potential source of new antimalarial drugs as they contain molecules with a great variety of structures and pharmacological activities.

**Summary** A large number of antimalarial compounds with a wide variety of structures have been isolated from plants and can play a role in the development of new antimalarial drugs. Ethnopharmacological approaches appear to be a promising way to find plant metabolites that could be used as templates for designing new derivatives with improved properties.

**Keywords** antiplasmodial; malaria; plant compounds; *Plasmodium falciparum*; traditional medicine

## Introduction

Malaria is a parasitic disease caused by *Plasmodium* species transmitted from the blood of an infected person and passed to a healthy human by a female *Anopheles* mosquito. There are four types of human malaria and *Plasmodium falciparum* is responsible for the most severe cases, and so most studies have evaluated the activity of compounds on this species. Malaria affects 350–500 million people per year worldwide and is responsible for 1.1 million deaths per year. In many parts of the world the parasites have developed resistance to a number of antimalarials such as chloroquine and derivatives, the most widely used treatment for malaria, and so there is an urgent need to discover new compounds with an original mode of action. Plants commonly used in traditional medicine are a source of active new compounds. For example, artemisinin isolated from *Artemisia annua* and used in China to treat malaria is a sesquiterpene lactone prescribed in combination therapies to fight chloroquino-resistant *P. falciparum*. In this review, all new active metabolites isolated from plants used in traditional medicine to treat malaria are described and organised according to their phytochemical classes. All the activities described were determined *in vitro* on *P. falciparum* strains, unless otherwise specified, and bio-guided fractionation was also based on this antimalarial test. Activities were assessed on different strains, among which are chloroquine sensitive (NF54, NF54/64, 3D7, D6, F32, D10, HB3, FCC1-HN, Ghana), chloroquine resistant (FcB1, W2, FCM29, BHz26/86, Dd2, EN36, ENT30, FCR3, FCR-3/A2) and/or multidrug resistant (K1, TM91C235) strains, to find effective compounds against resistant malaria. We considered that those having an IC50 ≤ 11 $\mu$M may have some interest for further development, while those with lower activity were less interesting. We only give structures for promising compounds, the others are cited in tables. As reviews already exist for compounds published before 2005,[1–7] we focused on those published from 2005 to the end of 2008. Some examples of recent natural antiplasmodial compounds are also cited in Mambu and Grellier[8] and, more recently, in Kaur *et al*.[9]

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## Phenolic derivatives

### *Flavonoid derivatives*

Bioassay-guided fractionation of the ethyl acetate extract of the leaves of *Piptadenia pervillei* Vatke (Leguminosae) led to the isolation of two phenolic compounds: (+)-catechin 5-gallate (**1**) and (+)-catechin 3-gallate (**2**). Compounds **1** and **2** displayed high activity, with IC50 values of 1.2 $\mu$M and 1.0 $\mu$M (FcB1), respectively, and no significant cytotoxicity.[10] New secondary metabolites were isolated from the root extract of *Bauhinia purpurea* L. (Leguminosae). Among the isolated metabolites, a flavanone exhibited moderate antimalarial activity, demethoxymatteucinol (**3**) (IC50 = 9.5 $\mu$M against K1).[11] Phytochemical investigation of the stem bark and root bark of *Friesodielsia obovata* (Benth.) Verdc. (Annonaceae) also afforded demethoxymatteucinol (**3**), which possessed weak antiplasmodial activity, with IC50 = 34.1 and 29.9 $\mu$M against K1 and NF54, respectively.[12] Investigation of the chemical constituents of the root bark of *Artocarpus rigidus* Blume subsp. *rigidus* (Moraceae) led to the isolation of two known flavonoids, artonin F (**4**) and cycloartobiloxanthone (**5**), which exhibited antiplasmodial activity against K1 (4.8 $\mu$M and 8.5 $\mu$M, respectively).[13] Two new prenylated flavones, artocarpones A (**6**) and B (**7**) (IC50 = 0.12 and 0.18 $\mu$M, respectively), and seven known prenylated flavonoids, including artonin A (**8**) (IC50 = 0.55 $\mu$M), cycloheterophyllin (**9**) (IC50 = 0.02 $\mu$M), artoindonesianin R (**10**) (IC50 = 0.66 $\mu$M), heterophyllin (**11**) (IC50 = 1.04 $\mu$M), heteroflavanone C (**12**) and artoindonesianin A-2 (**13**) (IC50 = 1.31 $\mu$M) were isolated from the stem bark of *Artocarpus champeden* Spreng. (Moraceae). The isolated compounds were tested for their inhibitory activity against 3D7. All possessed interesting activity with inhibitory concentrations from 0.001 to 1.31 $\mu$M. Compound **12** was the most potent with an IC50 of 1 nM. The inhibitory activity of these flavonoid derivatives supports the traditional use of the dried stem bark of *A. campeden* as an antimalarial drug.[14] Antitubercular and antimalarial activity-guided study of the dichloromethane extract of the roots of *Artocarpus altilis* (Parkinson) Fosberg (Moraceae) led to the isolation of nine prenylated flavones, including cycloartocarpin (**14**), artocarpin (**15**), chaplashin (**16**), morusin (**17**), cudraflavone B (**18**), artonin E (**19**) and artobiloxanthone (**20**). All compounds exhibited antiplasmodial activity against K1 with IC50 values of 9.9, 6.9, 7.7, 4.5, 5.2, 6.4 and 6.9 $\mu$M, respectively.[15] Ethyl acetate extract from the stem bark of *Erythrina fusca* Lour. (Leguminosae) showed antimalarial activity against K1, and lonchocarpol A (**21**) isolated from that extract showed notable antimalarial activity (IC50 = 3.9 $\mu$M). However, two others flavonoids isolated from the same sample did not show any activity, even though these compounds possessed prenylated substitution.[16] Isoflavonoids and flavonoids were isolated from the root bark and the stem bark of *Erythrina sacleuxii* Hua (Leguminosae). The two most active against D6 and W2 were 5′-prenylpratensein (**22**, IC50 on D6 = 6.3 $\mu$M and IC50 on W2 = 8.7 $\mu$M) and shinpterocarpin (**23**, IC50 on D6 = 6.6 $\mu$M and IC50 on W2 = 8.3 $\mu$M).[17] Phytochemical investigation of the hexane and $CH_2Cl_2$ extracts of *Erythrina stricta* Roxb. (Leguminosae) roots and *Erythrina subumbrans* Merr. (Leguminosae) stems led to the isolation of two pterocarpans, erybraedin A (**24**) and erystagallin A (**25**), and one flavanone, 5-hydroxysophoranone (**26**). All of them exhibited reasonable antiplasmodial activity against K1 with IC50 = 8.7, 9.0 and 5.3 $\mu$M, respectively.[18] Vogelin C (**27**) and lespedezaflavanone B (**28**) were isolated from the bark of *Erythrina subumbrans* Merr. (Leguminosae) and possessed antiplasmodial activity against K1 with IC50 values of 6.6 and 9.1 $\mu$M, respectively.[19] A known compound, 6-prenylapigenin (**29**), was isolated from *Cannabis sativa* L. (Cannabaceae) and displayed notable antimalarial activity against D6 and W2 with IC50 values of 6.7 and 4.8 $\mu$M, respectively.[20] The 80% ethanol extract from the outer bark of *Ochna integerrima* Lour. (Merr.) (Ochnaceae) led to isolation of a biflavanone (**30**) that had not been found previously from a natural plant source and is a potent antimalarial ingredient against K1 (IC50 = 157 nM). The stereoisomer of **30** (**31**) was also isolated from this plant but its activity was significantly lower than that of **30** (IC50 = 10.2 $\mu$M).[21] The antiplasmodial activity of five natural biflavonoids was estimated on K1. Lanaroflavone (**32**) isolated from the aerial parts of *Campnosperma panamensis* Standl. (Anacardiaceae) showed the highest antiplasmodial activity (IC50 = 0.48 $\mu$M) and exhibited a high selectivity index value (SI = 159), indicating selective antiplasmodial activity. Ginkgetin (**33**), isoginkgetin (**34**), bilobetin (**35**) and sciadopitysin (**36**) isolated from the leaves of *Ginkgo biloba* L. (Ginkgoaceae) showed antiplasmodial activity (IC50 = 2.0, 3.5, 6.7 and 1.4 $\mu$M with SI = 4.1, 3.2, 4.0 and 49, respectively).[22,23] A new biflavanone, *ent*-naringeninyl-(I-3$\alpha$,II-8)-4′-*O*-methylnaringenin (**37**) was isolated from the root bark of *Garcinia livingstonei* T.Anderson (Clusiaceae) collected in Tanzania. This compound showed reasonable activity against Ghana strain (IC50 = 6.7 $\mu$M).[24] Phytochemical re-examination of the aerial exudates of *Polygonum senegalense* Meisn. (Polygonaceae) forma *senegalense* resulted in the isolation of two chalcones (**38** and **39**) active, respectively, with an IC50 of 3.1 $\mu$M on D6 and 2.4 $\mu$M on W2, and 14.0 $\mu$M on D6 and 9.5 $\mu$M on W2.[25] The bioassay-guided purification of an *n*-hexane extract from the leaves of *Piper hostmannianum* C.DC. var. *berbicense* (Piperaceae) led to the isolation of four monoterpenes or prenyl-substituted dihydrochalcones as well as known compounds. (–)-Methyllinderatin (**40**) and linderatone (**41**) exhibited moderate antiplasmodial activity with IC50 values of 5.6 and 5.3 $\mu$M (**40**) and 10.3 and 15.1 $\mu$M (**41**), respectively, against F32 and FcB1. The activity of **40** was confirmed *in vivo* against *Plasmodium vinckei petteri* in mice (80% reduction of parasitemia) at a dose of 20 mg/kg per day intraperitonally.[26] A prenylated chalcone, medicagenin (**42**), was isolated from *Crotalaria medicagenia* Lam. (Leguminosae). Antimalarial activity was evaluated against NF-54 and medicagenin exhibited 100% inhibition of schizont maturation at a concentration of 2 $\mu$g/ml.[27] A prenylated chalcone, bartericin A (**43**), and three known natural products, stipulin (**44**), 4-hydroxylonchocarpin (**45**) and kanzonol B (**46**) were isolated from the twigs of *Dorstenia barteri* var. *subtriangularis* (Engl.) Hijman & C.C. Berg (Moraceae). These compounds were evaluated against

W2 and found to be moderately active (IC50 = 2.2, 5.1, 3.4 and 9.6 $\mu$M, respectively).[28] Bioassay-directed fractionation of the EtOAc extract of the stem bark of *Hintonia latiflora* (Sessé & Moc. ex DC.) Bullock (Rubiaceae), using the in-vitro 16-h and the in-vivo 4-day suppression tests on *Plasmodium berghei* schizont numbers, led to the isolation of the new 5-*O*-$\beta$-D-glucopyranosyl-7,4′-dimethoxy-3′-hydroxy-4-phenylcoumarin, along with the known 5-*O*-$\beta$-D-glucopyranosyl-7-methoxy-3′,4′-dihydroxy-4-phenylcoumarin. Both compounds suppressed the development of *P. berghei* schizonts with IC50 values of 24.7 and 25.9 $\mu$M, respectively, and the latter compound suppressed the development of schizonts by 70.8% at an oral dose of 40 mg/kg in the in-vivo assay.[29]

Figure 1 shows the flavonoid derivatives with moderate or promising activity *in vitro* against various strains of *P. falciparum.*

### Xanthones

The methanol extract of the stem bark of *Allanblackia monticola* Mildbr. (Clusiaceae) resulted in the isolation of a new prenylated xanthenedione, designated as allanxanthone C (**47**), together with the known compounds norcowanin (**48**), mangostin (**49**) and tovophyllin A (**50**). Compounds were assayed for their antiplasmodial activity and for their cytotoxicity. Three of these compounds (**47**–**49**) were found to be active against *Plasmodium*: **47**, IC50 on FcM29 = 1.3 $\mu$M and IC50 on F32 = 6.9 $\mu$M; **48**, not tested on FcM29 and IC50 on F32 = 6.3 $\mu$M; **49**, IC50 on FcM29 = 4.1 $\mu$M and IC50 on F32 = 7.8 $\mu$M, and also showed weak cytotoxicity against human melanoma A375 cells.[30] Tovophyllin A (**50**) was the most interesting with promising antimalarial activity (IC50 on FcM29 = 0.7 $\mu$M and IC50 on F32 = 20.3 $\mu$M) and relatively low cytoxicity.[31] A new prenylated xanthone, 5-*O*-methylcelebixanthone (**51**), together with a known compound, cochinchinone C (**52**), were isolated from roots of *Cratoxylum cochinchinense* Blume (Clusiaceae). Compounds **51** and **52** exhibited antimalarial activity against K1 with IC50 values of 8.9 and 6.3 $\mu$M, respectively. IC50 values for cytotoxicity were within the range of 5.6 $\mu$M for **52**. No cytotoxicity was observed with **51**.[32] A xanthone derivative, gaboxanthone (**53**), was isolated from the seed shells of *Symphonia globulifera* L.f. (Clusiaceae), together with known compounds, symphonin (**54**) and globuliferin (**55**). The antiplasmodial activity of the phenolic compounds was evaluated against W2. Compounds **53**–**55** gave IC50 values of 3.5, 1.3 and 3.9 $\mu$M, respectively.[33] The whole plant of *Swertia alata* Royle ex D.Don (Gentianaceae) was investigated and three xanthones, swertiaperennine, swertianin and decussatin, were isolated and tested for antimalarial activity. The results indicated that all xanthones possessed superior IC50 values at 50 $\mu$M. However, swertiaperennine was tested *in vivo* in the *P. berghei* test model and reduced parasitemia by 17.60% at a dose of 10 mg/kg.[34] A new compound, garciniaxanthone (**56**), was isolated from the roots of *Garcinia polyantha* Oliv. (Clusiaceae), in addition to three known compounds, smeathxanthone A (**57**), smeathxanthone B (**58**) and chefouxanthone (**59**). They exhibited antimalarial activity against NF54 with IC50 values ranging from 2.5 to 4.1 $\mu$M.[35]

Figure 2 shows xanthones with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### Stilbenes

A new stilbene glycoside, piceid-(1→6)-$\beta$-D-glucopyranoside (**60**), was isolated from the MeOH extract of the leaves of *Parthenocissus tricuspidata* Planch. (Vitaceae) together with three known compounds, piceid (IC50 = 13.2 $\mu$M), longistylin A (IC50 = 34.3 $\mu$M) and longistylin C (IC50 = 19.2 $\mu$M). The antiplasmodial activity of isolated compounds was determined *in vitro* against D10. Among the compounds isolated, **60** was the best inhibitor with an IC50 value of 5.3 $\mu$M.[36] Compound **60** was tested *in vivo* against *P. berghei* in mice intraperitoneally and exhibited significant blood schizontocidal activity in 4-day early infection, in preventive and curative treatment, with chemosuppression of 59 and 44% at 5 mg/kg per day, respectively, and an LD50 > 500 mg/kg.[37] A stilbene glycoside was isolated from an *n*-butanol-soluble fraction of the root of *Pleuropterus ciliinervis* Nakai (Polygonaceae). The compound was identified as (*E*)-resveratrol-3-*O*-$\alpha$-L-rhamnopyranosyl-(1-2)-$\beta$-D-xylopyranoside (**61**). It showed only moderate cytotoxicity and antimalarial activity against D10 with an IC50 of 3.9 $\mu$M.[38] Compound **61** was also found to have moderate antimalarial activity *in vivo* when tested against *P. berghei* in mice intraperitoneally. It possessed useful blood schizontocidal effects when used at doses that cause no marked toxicity in mice.[39]

Figure 3 shows stilbenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### Coumarins

Biologically guided fractionation of the methanolic extract of the roots of *Zanthoxylum flavum* Vahl. (Rutaceae) led to the isolation of isoimperatorin (**62**) which displayed IC50 values of 5.5 and 2.7 $\mu$M against D6 and W2, respectively.[40] A new coumarinolignan was isolated from a sample of *Grewia bilamellata* Gagnep. (Tiliaceae), grewin (**63**), which displayed antimalarial activity against D6 and W2 (IC50 11.2 $\mu$M and 5.5 $\mu$M, respectively) without significant cytotoxicity.[41] The compound 1-*O*-galloyl-6-*O*-luteoyl-$\alpha$-D-glucose (**64**) with an IC50 value of 2.21 $\mu$M (FCR3) was isolated from the boiled aqueous extract of the whole plant of *Phyllanthus niruri* L. (Euphorbiaceae).[42]

Figure 4 shows coumarins with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### Lignans

From the hexane extract of *Holostylis reniformis* Duch. (Aristolochiaceae), five lignans were isolated: (7′*R*,8*S*,8′*R*)-4,5-dimethoxy-3′,4′-methylenodioxy-2,7′-cyclolignan-7-one (**65**) (IC50 = 0.26 $\mu$M), (7′*R*,8*S*,8′*R*)-3′,4,4′,5-tetramethoxy-2,7′-cyclolignan-7-one (**66**) (IC50 = 0.32 $\mu$M), (7′*R*,8*R*,8′*S*)-3′,4,4′,5-tetramethoxy-2,7′-cyclolignan-7-one (**67**) (IC50 = 0.20 $\mu$M), (7′*R*,8*S*,8′*S*)-3′,4,4′,5-tetramethoxy-2,7′-cyclolignan-7-one (**68**) (IC50 = 0.63 $\mu$M) and (7′*R*,8*S*,8′*S*)-3′,4′-dimethoxy-4,5-methylenodioxy-2,7′-cyclolignan-7-one (**69**) (IC50 = 8.00 $\mu$M). Most compounds possessed high antiplasmodial activity against BHz26/86 and low toxicity on hepatic cells. Therefore, these compounds are potential candidates for the development of antimalarial drugs.[43] Seven tetrahydrofuran lignans isolated from *Nectandra megapotamica* Mez (Lauraceae) were evaluated for their antimalarial activity.

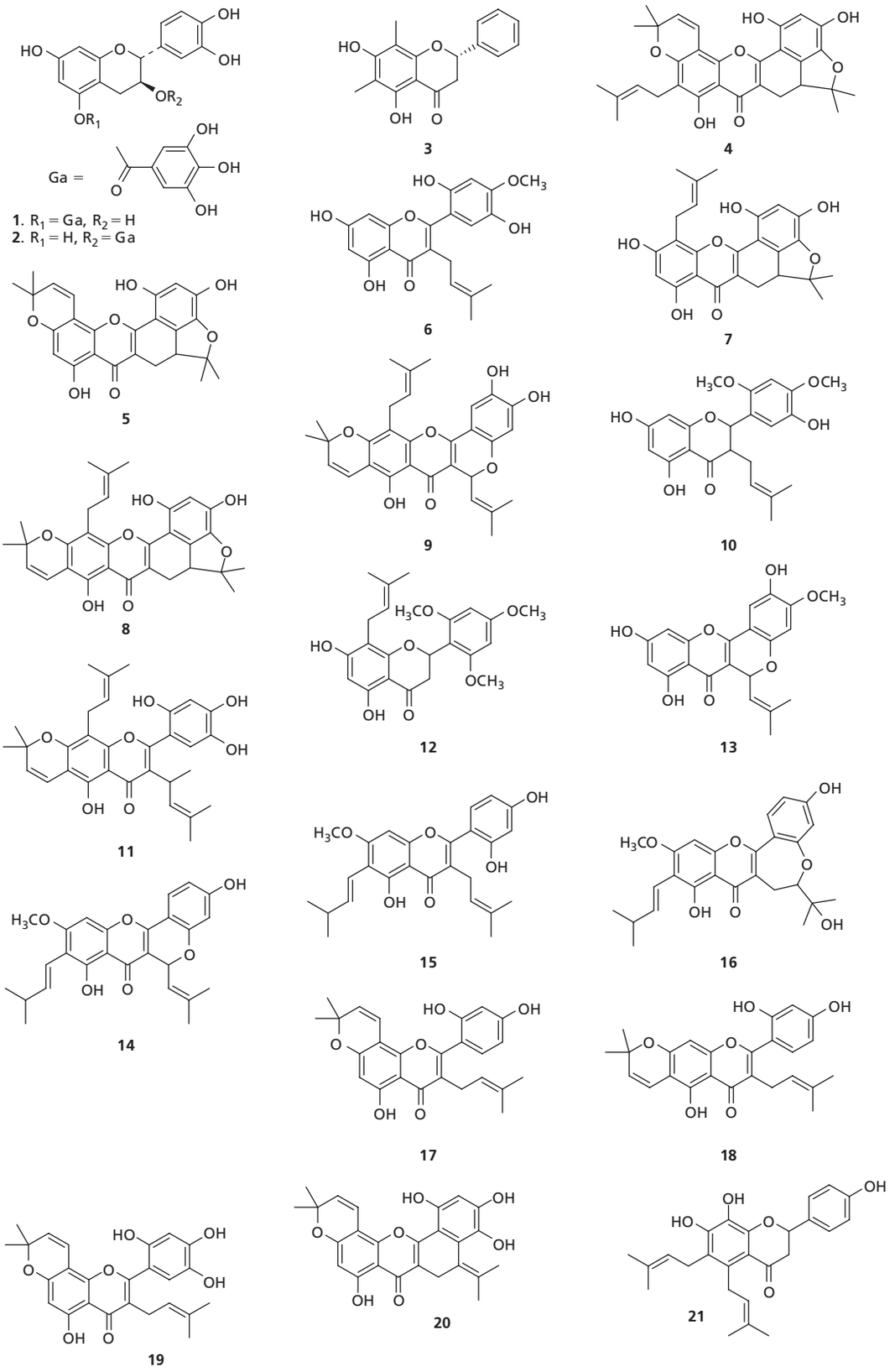



**Figure 1** Flavonoid derivatives with moderate or promising activity *in vitro* against various strains of *P. falciparum*

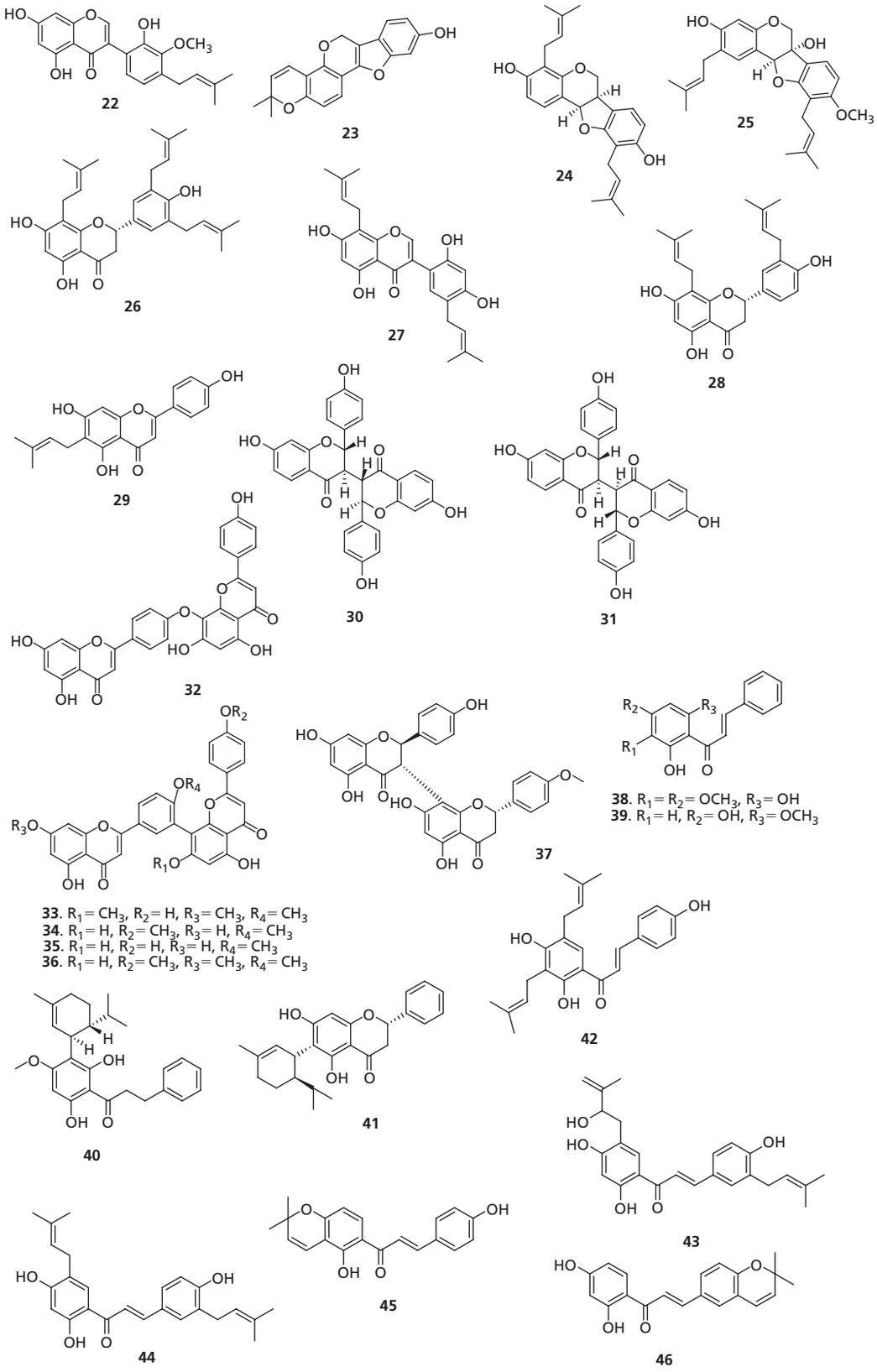



**Figure 1** (*Continued*)

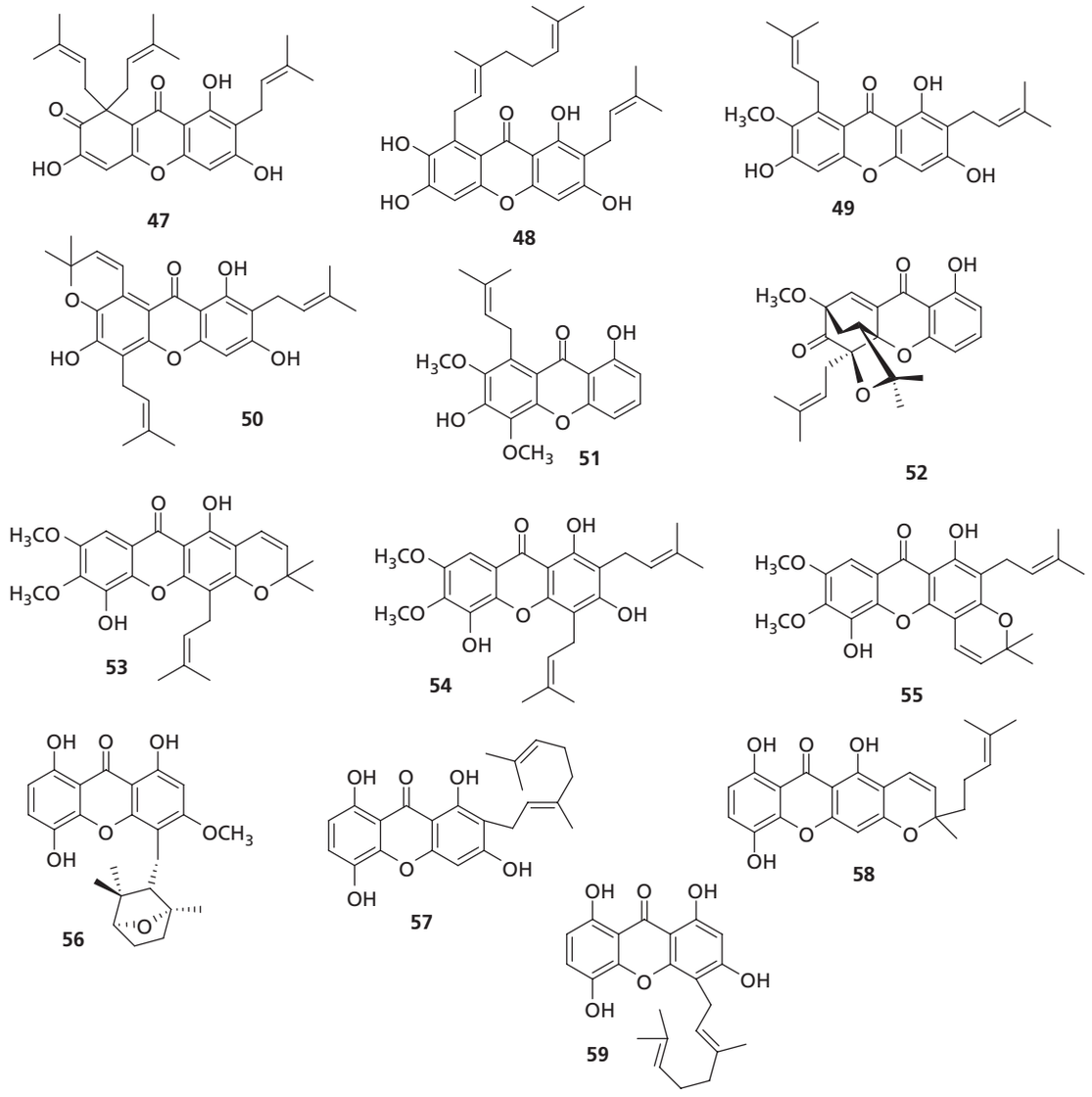



**Figure 2** Xanthones with moderate or promising activity *in vitro* against various strains of *P. falciparum*

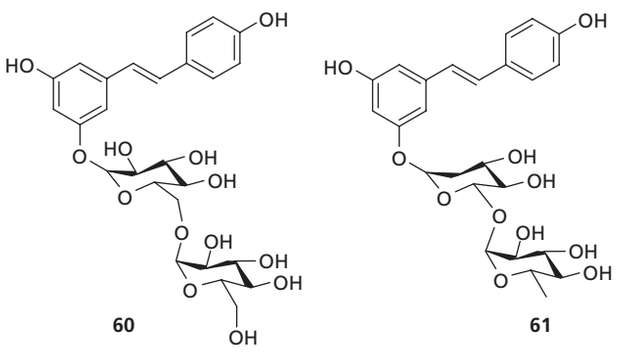



**Figure 3** Stilbenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*

Among the evaluated compounds, calopeptin (**70**) displayed moderate activity, with IC50 values of 10.7 $\mu$M (D6 clone) and 11.0 $\mu$M (W2 clone), and no cytotoxicity.[44] Bioassay-directed fractionation of the antimalarial active $CHCl_3$ extract of the dried stems of *Rourea minor* (Gaertn.) Aubl. (Connaraceae) liana led to the isolation of rourinoside (**71**). This lignan showed activity with an IC50 value of 3.7 $\mu$M against D6 and 2.1 $\mu$M against W2 strains.[45]

Figure 5 shows lignans with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

## Tannins

Partitioning of extracts of *Punica granatum* L. (Lythraceae) led to the isolation of ellagic acid, gallagic acid (**72**), punicalin and punicalagin (**73**). Gallagic acid and punicalagin exhibited moderate antiplasmodial activity against D6 (IC50 of 10.9 and 10.6 $\mu$M) and W2 clones (IC50 of 7.5 and 8.8 $\mu$M).[46]

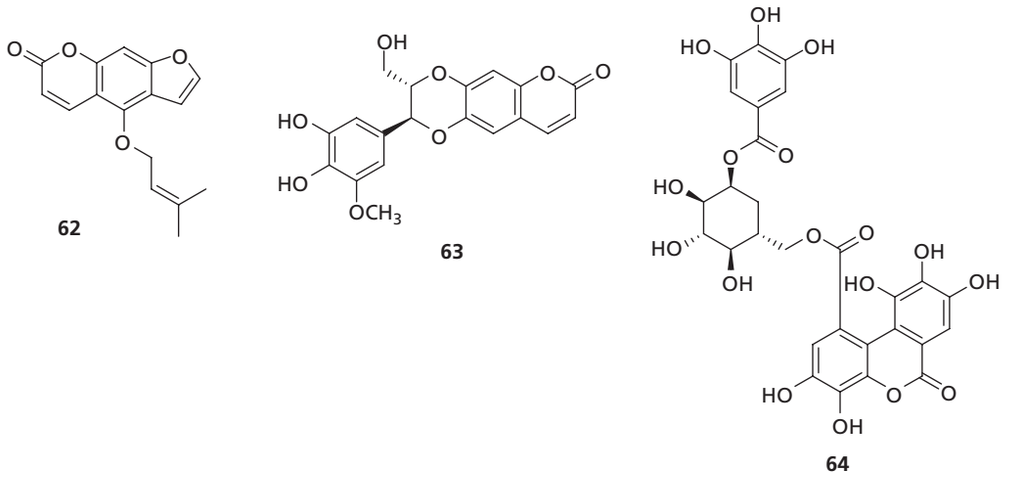



**Figure 4** Coumarins with moderate or promising activity *in vitro* against various strains of *P. falciparum*

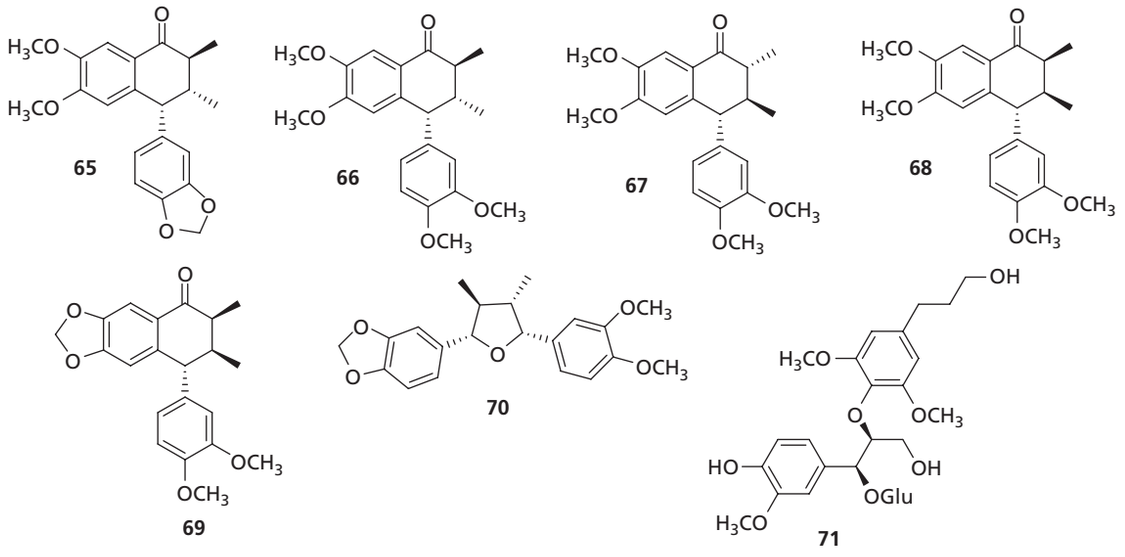



**Figure 5** Lignans with moderate or promising activity *in vitro* against various strains of *P. falciparum*

Figure 6 shows tannins with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### *Other phenolic derivatives*

The petroleum ether extract of *Viola websteri* Hemsl. (Violaceae) was investigated and the main antiplasmodial compound was 6-(8′*Z*-pentadecenyl)-salicylic acid (**74**) with an IC50 of 10.1 $\mu$M (D10).[47] Dictyochromenol (**75**) and a known compound, 2′*E*,6′*E* 2-farnesyl hydroquinone (**76**) obtained from the petroleum ether extract of the whole plant of *Piper tricuspe* C.DC. (Piperaceae) showed antimalarial activity against FcB1 with IC50 values of 9.58 and 1.37 $\mu$M while the selectivity index suggests their high toxicity.[48] 4-Nerolidylcatechol (**77**), isolated from the roots of *Pothomorphe peltata* (L.) Miq. (Piperaceae) presented significant inhibition (more active than quinine and chloroquine) against K1 (IC50 = 0.67 $\mu$M).[49] A new bischromone, chrobisiamone A (**78**), was isolated from the leaves of *Cassia siamea* Lam. (Leguminosae). Compound **78** displayed antiplasmodial activity against 3D7 with an IC50 of 5.6 $\mu$M.[50] A new cannabichromanone A derivative was isolated along with the known cannabichromanone C (**79**) from *Cannabis sativa* L. (Cannabaceae). Cannabichromanone A showed mild antimalarial activity against D6 and W2 clones with IC50 values of 11.1 and 11.4 $\mu$M, respectively, while cannabichromanone C had IC50 values of 13.1 and 9.4 $\mu$M, respectively.[51] Guttiferone A (**80**) was isolated from the seed shells of *Symphonia globulifera* L.f. (Clusiaceae). The antiplasmodial activity of compound **80** was evaluated against W2 and gave an IC50 value of 3.2 $\mu$M.[33] Isoxanthochymol (**81**) was isolated from the roots of *Garcinia polyantha* Oliv. (Clusiaceae) and exhibited antimalarial activity against NF54 with an IC50 of 2.2 $\mu$M.[35]

Figure 7 shows other phenolic derivatives with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

Table 1 gives the tested phenolic derivatives presenting low or no activity *in vitro* against various strains of *P. falciparum*.[12,13,16,17,25,26,28,29,32,34,37,40–42,47,48,50–66]

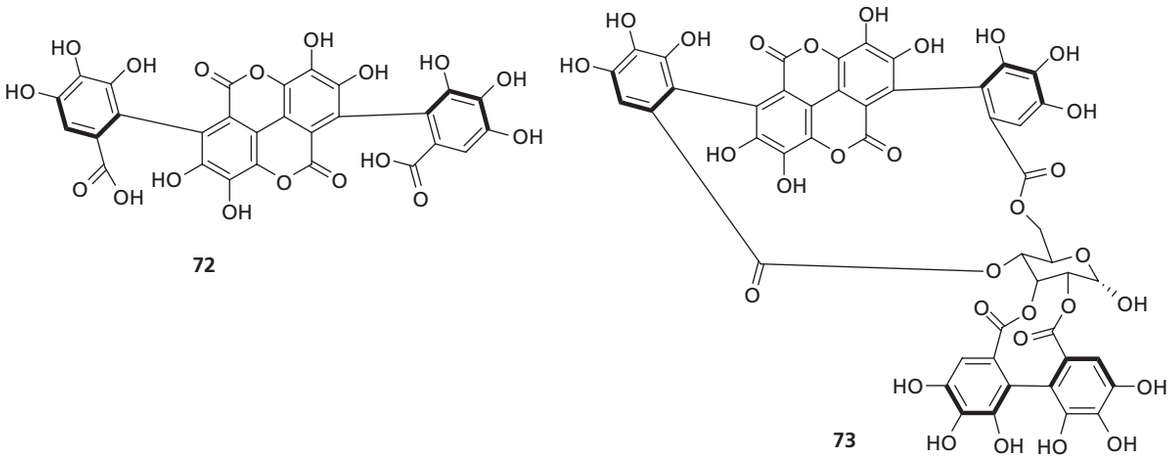



**Figure 6** Tannins with moderate or promising activity *in vitro* against various strains of *P. falciparum*

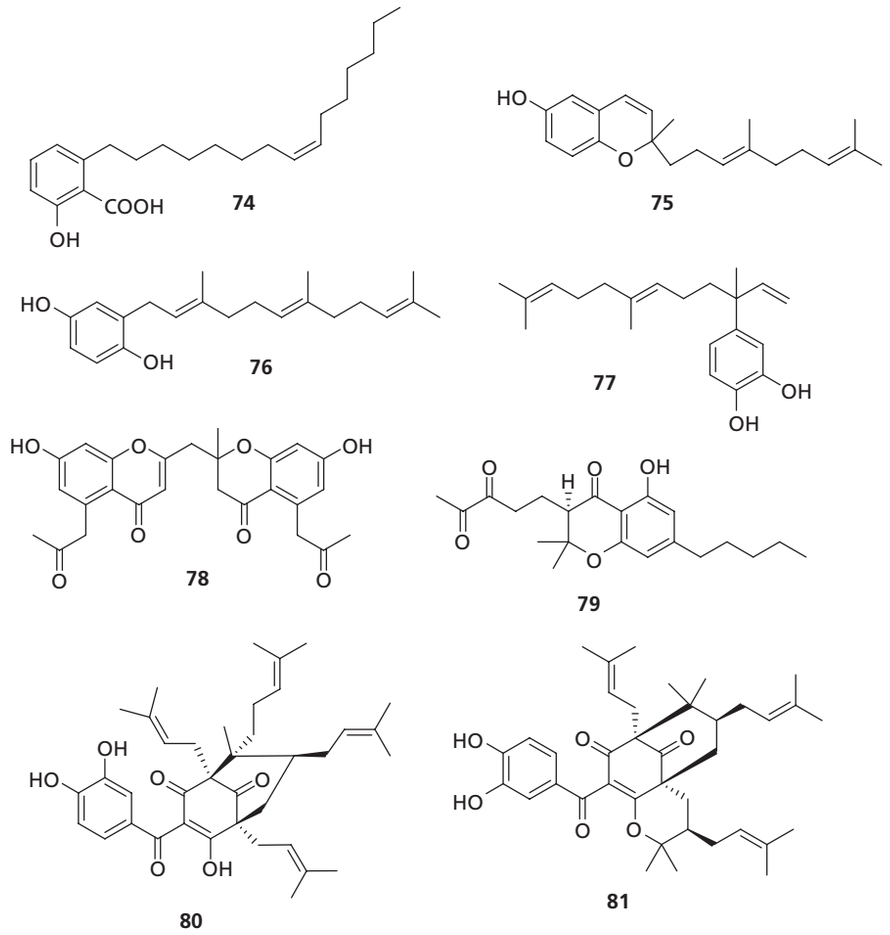



**Figure 7** Other phenolic derivatives with moderate or promising activity *in vitro* against various strains of *P. falciparum*

**Table 1** Phenolic derivatives presenting low or no activity *in vitro* against various strains of *P. falciparum*

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| Lawinal | *Friesodielsia obovata* (Benth.) Verdc. | Annonaceae | 27.5 (K1)<br>119.1 (NF54) | 12 |
| 2′,4′-Dihydroxy-3′-(2-hydroxybenzyl)-6′-methoxychalcone | *Ellipeiopsis cherrevensis* (Pierre ex Finet & Gagnep.) R.E.Fr. | Annonaceae | 18.9 (K1) | 52 |
| Syringic acid | *Commiphora opobalsamum* Engl. | Burseraceae | 17.7 (D6)<br>16.2 (W2) | 53 |
| Cannabichromanone A | *Cannabis sativa* L. | Cannabaceae | 11.1 (D6)<br>11.4 (W2) | 51 |
| Celebixanthone | *Cratoxylum cochinchinense* Blume | Clusiaceae | 14.3 (K1) | 32 |
| $\beta$-Mangostin | *Cratoxylum cochinchinense* Blume | Clusiaceae | 16.9 (K1) | 32 |
| 1,5-Dihydroxy-3-methoxy-4-isoprenylxanthone | *Chrysochlamys tenuis* Hammel | Clusiaceae | 31 (W2) | 54 |
| 1,3,7-Trihydroxy-2,4-diisoprenylaxnthone | *Chrysochlamys tenuis* Hammel | Clusiaceae | 20 (W2) | 54 |
| Toxyloxanthone A | *Chrysochlamys tenuis* Hammel | Clusiaceae | 16 (W2) | 54 |
| Combretastatin D-3 | *Getonia floribunda* Roxb. | Combretaceae | – | 55 |
| Combretastatin D-4 | *Getonia floribunda* Roxb. | Combretaceae | – | 55 |
| 3,5-Di-*O*-galloylquinic acid | *Sloanea rhodantha* (Baker) Capuron var. *rhodantha* | Elaeocarpaceae | 31.7 (HB3)<br>23.6 (FcM29) | 56 |
| 1,6-Di-*O*-galloyl glucopyranoside | *Sloanea rhodantha* (Baker) Capuron var. *rhodantha* | Elaeocarpaceae | 35.5 (HB3)<br>15.7 (FcM29) | 56 |
| 3,4,5-Tri-*O*-galloylquinic acid | *Sloanea rhodantha* (Baker) Capuron var. *rhodantha* | Elaeocarpaceae | 35.3 (HB3)<br>23.1 (FcM29) | 56 |
| 1,2,3,6-Tetra-*O*-galloyl glucopyranoside | *Sloanea rhodantha* (Baker) Capuron var. *rhodantha* | Elaeocarpaceae | 20.2 (HB3)<br>20.6 (FcM29) | 56 |
| 3-*O*-$\beta$-D-Glucopyranosyl-(2→1)-*O*-$\beta$-D-xylopyranoside | *Phyllanthus niruri* L. | Euphorbiaceae | 18.5 (FCR3) | 42 |
| $\beta$-Glucogallin | *Phyllanthus niruri* L. | Euphorbiaceae | 14.6 (FCR3) | 42 |
| (*E*)-3-(4-Methoxy-phenyl)-2-phenyl-acrylic acid | *Croton lobatus* L. | Euphorbiaceae | 19.1 (K1) | 57 |
| Swertiaperennine | *Swertia alata Royle ex D.Don* | Gentianaceae | >50 | 34 |
| Swertianin | *Swertia alata Royle ex D.Don* | Gentianaceae | >50 | 34 |
| Decussatin | *Swertia alata Royle ex D.Don* | Gentianaceae | >50 | 34 |
| Luteolin | *Satureja parvifolia* (Phil.) Epling | Lamiaceae | 22.3 (K1) | 58 |
| Lupinifolin | *Erythrina fusca* Lour. | Leguminosae | 30.8 (K1) | 16 |
| Citflavanone | *Erythrina fusca* Lour. | Leguminosae | 14.8 (K1) | 16 |
| 8-Prenyldaidzein | *Erythrina fusca* Lour. | Leguminosae | 12.1 (K1) | 16 |
| 5-Deoxy-3′-prenylbiochanin | *Erythrina sacleuxii* Hua | Leguminosae | 17.6 (D6)<br>22.5 (W2) | 17 |
| Corylin | *Erythrina sacleuxii* Hua | Leguminosae | 16.6 (D6)<br>19.7 (W2) | 17 |
| Erysubin F | *Erythrina sacleuxii* Hua | Leguminosae | 12.0 (D6)<br>12.8 (W2) | 17 |
| 3′-Prenylbiochanin A | *Erythrina sacleuxii* Hua | Leguminosae | 23.7 (D6)<br>28.4 (W2) | 17 |
| 7-Demethylrobustigenin | *Erythrina sacleuxii* Hua | Leguminosae | 27.2 (D6)<br>31.7 (W2) | 17 |
| 5′-Formylpratensein | *Erythrina sacleuxii* Hua | Leguminosae | 21.7 (D6)<br>27.9 (W2) | 17 |
| 2,3-Dehydrokeivetone | *Erythrina sacleuxii* Hua | Leguminosae | 15.1 (D6)<br>12.7 (W2) | 17 |
| Prostratol C | *Erythrina sacleuxii* Hua | Leguminosae | 17.6 (D6)<br>19.8 (W2) | 17 |
| Saclenone | *Erythrina sacleuxii* Hua | Leguminosae | 24.2 (D6)<br>22.6 (W2) | 17 |
| 2,3-Dihydro-7-demethylrobustigenin | *Erythrina sacleuxii* Hua | Leguminosae | 28.0 (D6)<br>31.8 (W2) | 17 |
| (3*R*)-7-Hydroxy-3′,4′-dimethoxyisoflavan-2′,5′-quinone | *Colutea istria* Mill. | Leguminosae | >50 (D6, W2) | 59 |
| 6,3′-Dihydroxy-7,4′-dimethoxyisoflavone | *Colutea istria* Mill. | Leguminosae | >50 (D6, W2) | 59 |

(*Continued*)

**Table 1** (*Continued*)

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| 2′-Methoxy-4′,5′-methylenedioxy-7,8-[2-(1-methylethenyl)furo]isoflavone | *Millettia puguensis* J.B.Gillett | Leguminosae | >50 | 60 |
| (–)-Maackiain | *Millettia puguensis* J.B.Gillett | Leguminosae | >50 | 60 |
| 6,7-Dimethoxy-3′,4′-methylenedioxyisoflavone | *Millettia puguensis* J.B.Gillett | Leguminosae | >50 | 60 |
| 7,2′-Dimethoxy-4′,5′-methylenedioxyisoflavone | *Millettia puguensis* J.B.Gillett | Leguminosae | >50 | 60 |
| 5-Acetonyl-7-hydroxy-2-methylchromone | *Cassia siamea* Lam. | Leguminosae | 19.4 (3D7) | 50 |
| Anhydrobarakol | *Cassia siamea* Lam. | Leguminosae | 36.4 (3D7) | 50 |
| 7-Demethylartonol E | *Artocarpus rigidus* Blume subsp. *rigidus* | Moraceae | 18.0 (K1) | 13 |
| Bartericin B | *Dorstenia barteri* var. *subtriangularis* (Engl.) Hijman & C.C.Berg | Moraceae | 19.3 (W2) | 28 |
| Isobavachalcone | *Dorstenia barteri* var. *subtriangularis* (Engl.) Hijman & C.C.Berg | Moraceae | 19.0 (W2) | 28 |
| Talaumidin | *Pycnanthus angolensis* (Welw.) Warb. | Myristicaceae | 60.5 (Dd2) | 61 |
| 5-Galloylquercetin-3-*O*-*R*-*L*-arabinofuranoside | *Calycolpus warscewiczianus* O.Berg | Myrtaceae | 14.5 (W2) | 62 |
| 2′,6′-Dihydroxy-4′-methoxydihydrochalcone | *Piper hostmannianum* C.DC. var. *berbicense* | Piperaceae | 12.7 (F32)<br>16.9 (FcB1) | 26 |
| 3-Farnesyl-*p*-hydroxybenzoic acid | *Piper tricuspe* C.DC. | Piperaceae | 29.78 (FcB1) | 48 |
| Polygohomoisoflavanone | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 19.2 (D6)<br>18.2 (W2) | 25 |
| 2-Propen-1-one,1-(2,4-dihydroxy-3,6-dimethoxyphenyl)-3-phenyl- | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 16.6 (D6)<br>17.8 (W2) | 25 |
| 2-Propen-1-one, 1-(2-hydroxy-4,6-dimethoxyphenyl)-3-phenyl- | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 15.7 (D6)<br>11.3 (W2) | 25 |
| 1-Propanone, 1-(2,6-dihydroxy-4-methoxyphenyl)-3-phenyl- | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 23.5 (D6)<br>22.8 (W2) | 25 |
| 1-Propanone, 1-(2,6-dihydroxy-3,4-dimethoxyphenyl)-3-phenyl- | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 11.8 (D6)<br>12.9 (W2) | 25 |
| 4*H*-1-Benzopyran-4-one,2,3-dihydro-5-hydroxy-7-methoxy-2-phenyl- | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 16.3 (D6)<br>21.8 (W2) | 25 |
| 2-Propen-1-one,1-(2,4-dihydroxy-6-methoxyphenyl)-3-phenyl- | *Polygonum senegalense* Meisn. forma *senegalense* | Polygonaceae | 14.0 (D6)<br>9.5 (W2) | 25 |
| Quercetin | *Morinda morindoides* (Baker) Milne-Redh. | Rubiaceae | 18.2 (K1) | 63 |
| 5-*O*-$\beta$-D-Glucopyranosyl-7,4′-dimethoxy-3′-hydroxy-4-phenylcoumarin | *Hintonia latiflora* (Sessé & Moc. ex DC.) Bullock | Rubiaceae | 24.7 (*P. berghei*) | 29 |
| 5-*O*-$\beta$-D-Glucopyranosyl-7-methoxy-3′,4′-dihydroxy-4-phenylcoumarin | *Hintonia latiflora* (Sessé & Moc. ex DC.) Bullock | Rubiaceae | 25.9 (*P. berghei*) | 29 |
| Bipinnatones A | *Boronia bipinnata* Lindl. | Rutaceae | 64 (Hbase II assay) | 64 |
| Bipinnatones B | *Boronia bipinnata* Lindl. | Rutaceae | 51 (Hbase II assay) | 64 |
| Bergapten | *Zanthoxylum flavum* Vahl. | Rutaceae | 21.8 (W2) | 40 |
| Syringaldehyde | *Vepris uguenensis* Engl. | Rutaceae | 71.4 (3D7)<br>117.6 (FcM29) | 65 |
| Greveichromenol | *Harrisonia perforata* Merr. | Simaroubaceae | 38.3 (K1) | 66 |
| Nitidanin | *Grewia bilamellata* Gagnep. | Tiliaceae | 21.2 (D6)<br>18.4 (W2) | 41 |
| 6-(8′*Z*,11′*Z*,14′*Z*-Heptadecatrienyl)-salicylic acid | *Viola websteri* Hemsl. | Violaceae | 13.3 (D10) | 47 |
| Piceid | *Parthenocissus tricuspidata* Planch. | Vitaceae | 13.2 (D10) | 37 |
| Longistylin A | *Parthenocissus tricuspidata* Planch. | Vitaceae | 34.3 (D10) | 37 |
| Longistylin C | *Parthenocissus tricuspidata* Planch. | Vitaceae | 19.2 (D10) | 37 |

## Quinones

Primin (**82**), a natural benzoquinone occurring in *Primula obconica* Hance. (Primulaceae), was investigated for its antiprotozoal potential. Compound **82** showed moderate activity against K1 with an IC50 of 10.9 $\mu$M.[67] A new non-cannabinoid constituent was isolated from *Cannabis sativa* L. (Cannabaceae) namely 5-acetoxy-6-geranyl-3-*n*-pentyl-1,4-benzoquinone (**83**), which displayed notable antimalarial activity against D6 and W2 clones with IC50 values of 7.5 and 7.0 $\mu$M, respectively.[20] New secondary

metabolites were isolated from the root extract of *Bauhinia purpurea* L. (Leguminosae). Among the isolated metabolites, two compounds exhibited antimalarial activity against K1, bauhinoxepin I (**84**) (IC50 = 10.5 μM) and bauhinoxepin J (**85**) (IC50 = 5.8 μM).[11] The ethanol extract of *Zhumeria majdae* Rech. f. & Wendelbo (Lamiaceae) showed potent antiplasmodial activity. Bioactivity-guided fractionation of the extract led to the isolation of 12,16-dideoxy aegyptinone B (**86**). This compound exhibited antiplasmodial activity with IC50 values of 4.4 and 4.7 μM against D6 and W2 strains, respectively. This compound was further found to have mild cytotoxicity towards cancer cell lines (IC50 = 15.2–50.6 μM).[68] From the roots of *Bulbine frutescens* Willd. (Asphodelaceae), the first sulfated phenylanthraquinones were isolated, together with their known sulfate-free analogues. Two of them, isoknipholone (**87**) and sodium 4′-*O*-demethylknipholone 6′-*O*-sulfate (**88**), presented promising activity against K1 with an IC50 of 0.28 μM for isoknipholone and an IC50 of 7.9 μM for the sulfated phenylanthraquinone.[69] From the roots of the African plant *Bulbine frutescens* Willd. (Asphodelaceae), two novel dimeric phenylanthraquinones, joziknipholones A (**89**) and B (**90**), were isolated. These two compounds exhibited strong activity against K1 with IC50 values of 164 and 270 nM, respectively.[70] Two compounds, 10-(chrysophanol-7′-yl)-10-(ξ)-hydroxychrysophanol-9-anthrone (**91**) and chryslandicin (**92**), were isolated from the dichloromethane extract of the roots of *Kniphofia foliosa* Hochst. (Asphodelaceae). They showed good activity against 3D7 with IC50 values of 0.5 and 1.0 μM, respectively.[71] Glaberianthrone (**93**), a new bianthrone, was isolated from the hexane extract of the stem bark of *Psorospermum glaberrimum* Hochr. (Clusiaceae) together with known compounds, 3-geranyloxyemodin anthrone (**95**), 3-prenyloxyemodin anthrone (**96**), 2-geranylemodin (**97**) and bianthrone 1a (**94**). Their IC50 values were 2.94, 1.68, 1.98, 5.34 and 2.53 μM, respectively, against the W2 strain.[72] Bazouanthrone (**98**), a new anthrone derivative, was isolated from the root bark of *Harungana madagascariensis* Poir. (Clusiaceae), together with known compounds, feruginin A (**99**), harunganin (**100**), harunganol A (**101**) and harunganol B (**102**). All the compounds were found to be moderately active against W2: **98**, IC50 = 1.8 μM; **99**, IC50 = 5.0 μM; **100**, IC50 = 2.7 μM; **101**, IC50 = 3.7 μM; **102**, IC50 = 3.7 μM.[73] To discover antimalarial substances from plants cultivated in Thailand, 80% EtOH extracts from selected plants were screened against K1 strain. *Polyalthia viridis* Craib (Annonaceae) was found to show notable antimalarial activity. Marcanine A (**103**) (IC50 = 10.5 μM) was identified as its major active constituent.[74]

Figure 8 shows quinones and derivatives with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

Table 2 gives the tested quinones presenting low or no activity *in vitro* against various strains of *P. falciparum*.[11,41,63,75,76]

## Terpenoid compounds

### *Sesquiterpenes*

Two sesquiterpenes, corymbolone (**104**) and mustakone (**105**), isolated from the chloroform extract of the rhizomes of *Cyperus articulatus* L. (Cyperaceae), exhibited antiplasmodial properties (IC50 = 4.53 and 0.64 μM against NF54 and IC50 = 8.14 and 1.15 μM against EN36, respectively).[77] *Oncosiphon piluliferum* (L.f.) Källersjö (Asteraceae) is used traditionally to treat a variety of ailments, mainly fevers. Sesquiterpene lactones of the germacranolide and eudesmanolide types displaying antiplasmodial activity against D10 were isolated and identified: sivasinolide (**106**, IC50 = 9.8 μM), tatridin A or tavulin (**107**, IC50 = 1.5 μM) and tanachin (**108**, IC50 = 1.5 μM). In addition, the cytotoxic effects of the active compounds against Chinese Hamster Ovarian cells were evaluated and the compounds were found to be toxic to mammalian cells at similar concentrations.[78] Two new helenanolide sesquiterpene lactones, helenalin-[2-(1-hydroxyethyl)acrylate] (**109**) and helenalin-[2-hydroxyethyl-3-methyl)acrylate] (**110**), as well as one known related structure, 11α,13-dihydrohelenalin-[2-(1-hydroxyethyl)acrylate] (**111**), were isolated from an ethyl acetate extract of leaves of *Vernoniopsis caudate* (Drake) Humbert (Asteraceae). The three lactones displayed strong antiplasmodial activity against FcB1, with IC50 values of 1, 0.19 and 0.41 μM, respectively. However, these compounds also exhibited considerable cytotoxicity on KB cells (IC50 < 1 μM in each case).[79] Leaves and flowers of *Artemisia gorgonum* Webb (Asteraceae) collected in Fogo, Cape Verde, were phytochemically investigated and resulted in the isolation of a known germacranolide, hanphyllin (**112**), which exhibited antiplasmodial activity with an IC50 of 9.7 μM against FcB1 and was weakly cytotoxic to the Vero cell line (IC50 = 111.9 μM).[80] Two new sesquiterpene lactones, wedelolides A (**113**) and B (**114**), were isolated from the leaves of *Wedelia trilobata* Hitchc. (Asteraceae). The two compounds displayed antimalarial activity with IC50 values of 4.2 and 9.1 μM, respectively.[81] A new sesquiterpene lactone as well as two known ones were isolated from the dichloromethane fraction of an aqueous extract from *Vernonia cinerea* Less. (Asteraceae). Three compounds, 8α-tigloyloxy-hirsutinolide-13-*O*-acetate (**115**), 8α-(4-hydroxyethacryloyloxy)-hirsutinolide-13-*O*-acetate (**116**) and vernolide D (**117**), were active against W2 with IC50 values of 3.9, 3.7 and 3.5 μM, respectively.[82] Fractionation of the dichloromethane extract of the leaves of *Vernonia staehelinoides* Mart. ex Baker (Asteraceae) allowed the isolation of two structurally related hirsutinolides. These compounds displayed strong antiplasmodial activity against D10 and were less effective against K1, compound **118**, 8α-(2-methylacryloyloxy)-3-oxo-1-desoxy-1,2-dehydrohirsutinolide-13-*O*-acetate had an IC50 = 0.6 μM on D10 and IC50 = 4.5 μM on K1 and compound **119**, 8α-(50-acetoxysenecioyloxy)-3-oxo-1-desoxy-1,2-dehydrohirsutinolide-13-*O*-acetate had an IC50/D10 = 0.5 μM and IC50/K1 = 5.5 μM. These two compounds were found to be cytotoxic to mammalian Chinese Hamster Ovarian cells at similar concentrations.[83] Chemical exploration of *Camchaya calcarea* Kitam. (Asteraceae) led to the isolation of eight known sesquiterpene lactones, which exhibited moderate antiplasmodial activity against K1, including goyazensolide (**120**) (IC50 = 3.3 μM), lychnophorolide B (**122**) (IC50 = 7.2 μM), isogoyazensolide (**123**) (IC50 = 4.4 μM), isocentratherin (**124**) (IC50 = 5.6 μM), 5-epi-isogoyazensolide (**125**) (IC50 = 4.4 μM) and 5-epi-isocentratherin (**126**) (IC50 = 8.0 μM). The most promising was lychnophorolide A (**121**) with an IC50 of

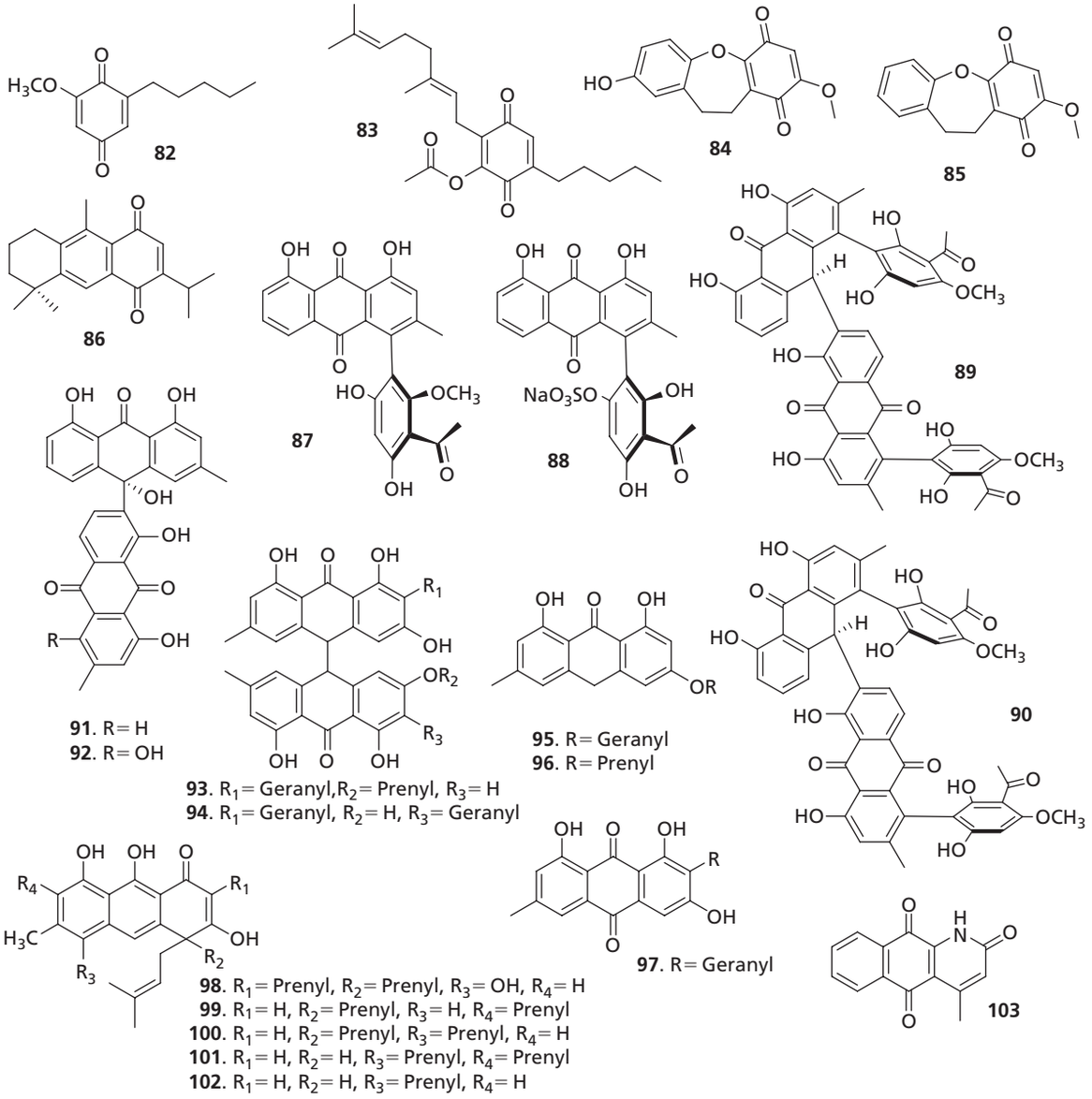



**Figure 8** Quinones and derivatives with moderate or promising activity *in vitro* against various strains of *P. falciparum*

**Table 2** Quinones presenting low or no activity *in vitro* against various strains of *P. falciparum*

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| Newbouldiaquinone A | *Newbouldia laevis* Seem. | Bignogniaceae | 78% at 20 $\mu$M (NF54) | 75 |
| Bauhinoxepin H | *Bauhinia purpurea* L. | Leguminosae | 11.2 (K1) | 11 |
| Rubiadin-1-methyl ether | *Prismatomeris malayana* Ridl. | Rubiaceae | – | 76 |
| Nordamnacanthal | *Prismatomeris malayana* Ridl. | Rubiaceae | – | 76 |
| Damnacanthal | *Prismatomeris malayana* Ridl. | Rubiaceae | – | 76 |
| Chrysarin | *Morinda morindoides* (Baker) Milne-Redh. | Rubiaceae | 105.4 (NF54/64) | 63 |
| Alizarin | *Morinda morindoides* (Baker) Milne-Redh. | Rubiaceae | 60.4 (NF54/64) | 63 |
| 2,6-Dimethoxy-1-acetonylquinol | *Grewia bilamellata* Gagnep. | Tiliaceae | 42.2 (D6)<br>23.0 (W2) | 41 |

0.8 $\mu$M.[84] Bioactivity-guided isolation of the chloroform fractions of the whole plants of *Carpesium rosulatum* Miq. (Asteraceae) led to the isolation of a sesquiterpene lactone, ineupatorolide A (**127**), displaying high antiplasmodial activity against D10 with an IC50 of 19 nM.[85] Ineupatorolide A was also found to have potential antimalarial activity *in vivo* when tested against *P. berghei* in mice. Compound **127** (2, 5, 10 mg/kg per day, intraperitoneally) exhibited a significant blood schizontocidal activity in 4-day early infection, preventive and curative treatment, with a significant mean survival time comparable with that of the standard drug, chloroquine (5 mg/kg per day). Ineupatorolide A possesses promising antiplasmodial activity that can be exploited in malaria therapy.[86] 4-Hydroxyanthecotulide (**128**), a linear sesquiterpene lactone isolated from *Anthemis auriculata* Boiss. (Asteraceae), was evaluated against K1 and had an IC50 of 7.6 $\mu$M.[87]

Figure 9 shows sesquiterpenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

## Diterpenes

Geranylgeraniol (**129**) was isolated from the stems and leaves of *Croton lobatus* L. (Euphorbiaceae), a medicinal plant used in western Africa in traditional folk medicine to cure malaria, pregnancy troubles and dysentery. The compound showed reasonable antiplasmodial activity against K1 with an IC50 value of 3.7 $\mu$M and good selectivity (SI value > 25).[57] A new diterpenoid, steenkrotin A (**130**), was isolated from an ethanol extract of the leaves of *Croton steenkampianus*

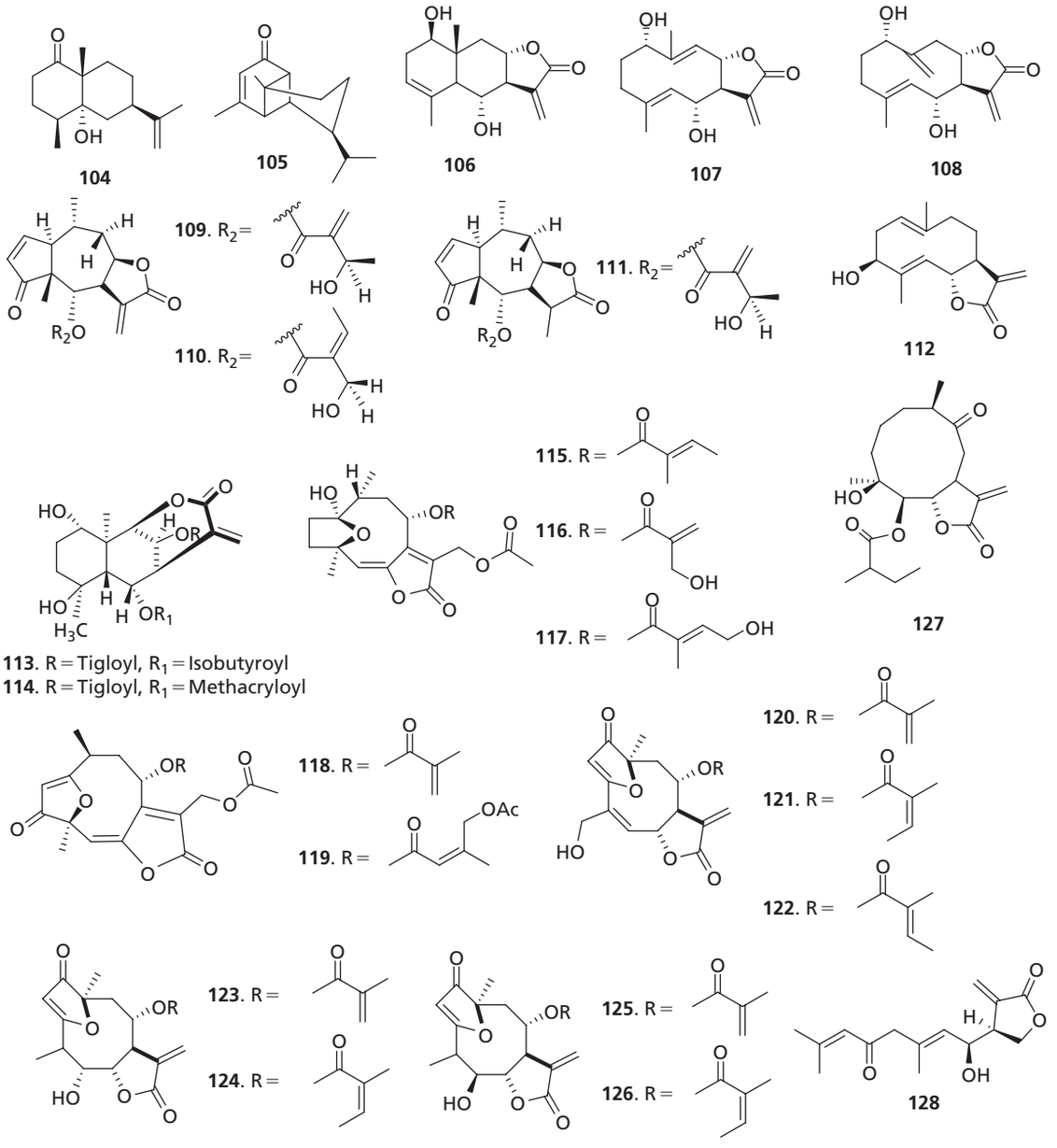



**Figure 9** Sesquiterpenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*

Gerstner (Euphorbiaceae) and was tested against D10, D6, Dd2 and W2, showing moderate activity with IC50 values of 15.8, >30, 9.4 and 9.1 $\mu$M, respectively.[88]

Labdane diterpenoid, 3-deoxyaulacocarpin A (**131**) was isolated from the seeds of *Aframomum zambesiacum* K. Schum (Zingiberaceae). It possessed antiplasmodial activity against FcB1 with an IC50 of 4.97 $\mu$M.[89] Known compounds were isolated from the dried fruits of *Juniperus seravschanica* Komarov (Cupressaceae) and were tested. Three of them showed promising antimalarial activity: cedrol (**132**) with IC50 = 265, 1.4 and 10.2 $\mu$M; sugiol (**133**) with IC50 = 1.6, 3.4 and 1.4 $\mu$M; and 12,15-dihydroxylabda-8 (17),13-dien-19-oic acid (**134**) with IC50 = 2.2, 4.1 and 4.6 $\mu$M against D6, TM91C235 and W2, respectively.[90] *Vitex rehmannii* Gürke (Lamiaceae) contained a labdane diterpene, 12*S*,16*S*/*R*-dihydroxy-*ent*-labda-7,13-dien-15,16-olide (**135**), which exists as an inseparable epimeric mixture. This mixture exhibited reasonable antimalarial activity against FCR-3 (IC50 = 7.2 $\mu$M). However, this was due to its cytotoxic properties.[91]

Bioassay-guided fractionation of a trunk bark extract of *Laetia procera* (Poepp.) Eichler (Flacourtiaceae) led to the isolation of six clerodane diterpenoids: casearlucin A (**136**), casamembrol A (**137**), laetiaprocerine A–D (**138–141**). The diterpenoids exhibited antiplasmodial activity with IC50 values of 0.62, 0.57, 0.58, 4.44, 4.66 and 6.04 $\mu$M on F32 strain, and 0.54, 0.59, 0.66, 6.08, 5.35, 3.79 and 27.5 $\mu$M on FCb1 strain, but most of them were also cytotoxic. Compound **138** showed the best selectivity index of 6.8.[92] Bioactivity-guided fractionation of hexane and dichloromethane extracts of the bark of *Casearia grewiifolia* Vent. (Flacourtiaceae) afforded four new clerodane diterpenes, caseargrewiins A–D (**142–145**), and two known clerodane diterpenes, *rel*-(2*S*,5*R*,6*R*,8*S*,9*S*,10*R*,18*S*,19*R*)-18,19-diacetoxy-18,19-epoxy-6-methoxy-2-(2-methylbutanoyloxy)cleroda-3,13 (16),14-triene (**146**) and *rel*-(2*S*,5*R*,6*R*,8*S*,9*S*,10*R*,18*S*,19*R*)-18,19-diacetoxy-18,19-epoxy-6-hydroxy-2-(2-methylbutanoyloxy)cleroda-3,13(16),14-triene (**147**). All compounds exhibited antimalarial activity against K1 with IC50 values of 5.5, 3.6, 5.2, 7.9, 6.0 and 6.0 $\mu$M, but also cytotoxicity.[93]

A new diterpene, (1*S*,5*S*,9*S*,10*S*,11*R*,13*R*)-1,11-dihydroxypimara-8(14),15-diene (**148**) was isolated from the dichloromethane extract of whole plants of *Kaempferia marginata* Carey (Zingiberaceae) and had antimalarial activity against K1 (IC50 = 10.5 $\mu$M).[94]

Some 44 cassane- and norcassane-type diterpenes isolated from $CH_2Cl_2$ extract of *Caesalpinia crista* L. (Caesalpiniaceae) from Myanmar and Indonesia were evaluated for their antimalarial activity against FCR-3/A2 clone. Caesalpinins MA (**149**), ME–MJ (**150–155**), ML (**156**), norcaesalpinins MC (**157**) and MD (**158**), caesalpinins C–F (**159–162**), J–K (**163–164**), N (**165**) and P (**166**), norcaesalpinins A–F (**167–172**), caesalmins B (**173**) and C (**174**), caesaldekarin E (**175**), 2-acetoxycaesaldekarin E (**176**), 2-acetoxy-3-deacetoxycaesaldekarin E (**177**), 14(17)-dehydrocaesalmin F (**178**), bonducellpins B (**179**) and C (**180**), 7-acetoxybonducellpin C (**181**) and 1-deacetoxy-1-oxocaesalmin C (**182**) displayed antimalarial activity with IC50 values of: 3.5, 3.6, 4.1, 2.5, 7.0, 2.1, 1.9, 0.65, 3.1, 1.0, 0.76, 0.8, 6.5, 0.65, 1.0, 0.40, 0.12, 1.7, 0.8, 0.26, 5.0, 2.0, 0.09, 0.14, 0.80, 3.4, 4.0, 6.5, 0.098, 0.2, 0.24, 0.12, 0.6 and 2.9 $\mu$M, respectively. Eighteen diterpenes possessed strong activity with IC50 $\leq$ 1 $\mu$M, with norcaesalpinin E (**171**) and 2-acetoxy-3-deacetoxycaesaldekarine (**177**) being the most potent.[95,96] In continuity with the previous work, a new furanocassane-type diterpene, caesalpinin H (**183**), was isolated from the $CH_2Cl_2$ extract of the seed kernels of *Caesalpinia crista* L. (Caesalpiniaceae) and showed an IC50 value of 5.2 $\mu$M against FCR-3/A2.[97] Three new cassane furanoditerpenoids were isolated from the EtOAc extract of the seed kernels of *Caesalpinia bonduc* L. Roxb. (Caesalpiniaceae). Bonducellpins E–G (**184–186**) exhibited antimalarial activity on K1 strain with IC50 values of 1.6, 5.8 and 3.8 $\mu$M, respectively. None of the compounds were cytotoxic against any of the tumour cell lines tested.[98] Compound 6$\alpha$,7$\beta$-diacetoxyvouacapane (**187**) was isolated from the seeds of *Bowdichia nitida* Spruce ex Benth. (Leguminosae), and showed promising antiplasmodial activity against 3D7 (IC50 = 968 nM) and a good selectivity index with regard to cytotoxicity (IC50 > 250 $\mu$M).[99] Bioactivity-guided fractionation of the petroleum ether extract of the leaves of *Hyptis suaveolens* (L.) Poit. (Lamiaceae), widely used in traditional medicine, led to the isolation of an abietane-type diterpenoid endoperoxide, 13$\alpha$-epi-dioxiabiet-8(14)-en-18-ol (**188**), displaying high antiplasmodial activity against D10 (IC50 = 344 nM).[100]

Five known abietane diterpenes (**189–193**) were isolated from five *Plectranthus* species (Lamiaceae), namely *Plectranthus hadiensis* C. Chr., *Plectranthus lucidus* Burch. ex Benth., *Plectranthus ecklonii* Benth., *Plectranthus purpuratus* Harv. subsp. *purpuratus* and *Plectranthus purpuratus* Harv. subsp. *tongaensis*. The compounds showed antiplasmodial activity against FCR-3 (IC50 = 4.6, 5.3, 3.1, 6.0 and 4.7 $\mu$M, respectively). However, the cytotoxicity profile indicated a low degree of specificity towards the malaria parasite.[101] A bioassay-guided fractionation of *Juniperus procera* Hochst. ex Endl. (Cupressaceae) berries yielded pure compounds. Among these, abieta-7,13-diene (**194**) and ferruginol (**195**) demonstrated antimalarial activity against D6 and W2 strains with IC50 = 7.0 and 7.4 $\mu$M, respectively, for **194** and IC50 = 12.3 and 4.9 $\mu$M, respectively, for **195**.[102]

In 2006, the antimalarial activity of ferruginol (IC50 = 6.9 $\mu$M) isolated from *Fuerstia africana* T.C.E.Fr. (Lamiaceae) was correlated with cytotoxic activity and, therefore, it was not a promising antimalarial candidate.[103]

Five new poly-*O*-acylated jatrophane diterpenes, including 1$\alpha$,13$\beta$,14$\alpha$trihydroxy-3$\beta$,7$\beta$-dibenzoyloxy-9$\beta$,15$\beta$-diacetoxyjatropha-5,11 *E*-diene (**196**), 1$\alpha$,8$\beta$,9$\beta$,14$\alpha$,15$\beta$-pentaacetoxy-3$\beta$-benzoyloxy-7-oxojatropha-5,12-diene (**197**), 7,8$\beta$,9$\beta$,14$\alpha$,15$\beta$-pentaacetoxy-3$\beta$-benzoyloxy-1$\alpha$,5$\beta$-dihydroxyjatropha-6(7),12-diene (**198**) and 1$\alpha$,7,8$\beta$,9$\beta$,14$\alpha$,15$\beta$-hexaacetoxy-3$\beta$-benzoyloxy-5$\beta$-hydroxyjatropha-6(7), 12-diene (**199**) were isolated from the white latex of *Pedilanthus tithymaloides* (L.) Poit. (Euphorbiaceae). These highly oxygenated diterpenes possess a rare *O*-acetyl enol moiety and showed antiplasmodial activity against K1 strain: **196** (IC50 = 5.9 $\mu$M), **197** (IC50 = 4.9 $\mu$M), **198** (IC50 = 6.0 $\mu$M) and **199** (IC50 = 5.8 $\mu$M).[104]

Figure 10 shows diterpenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

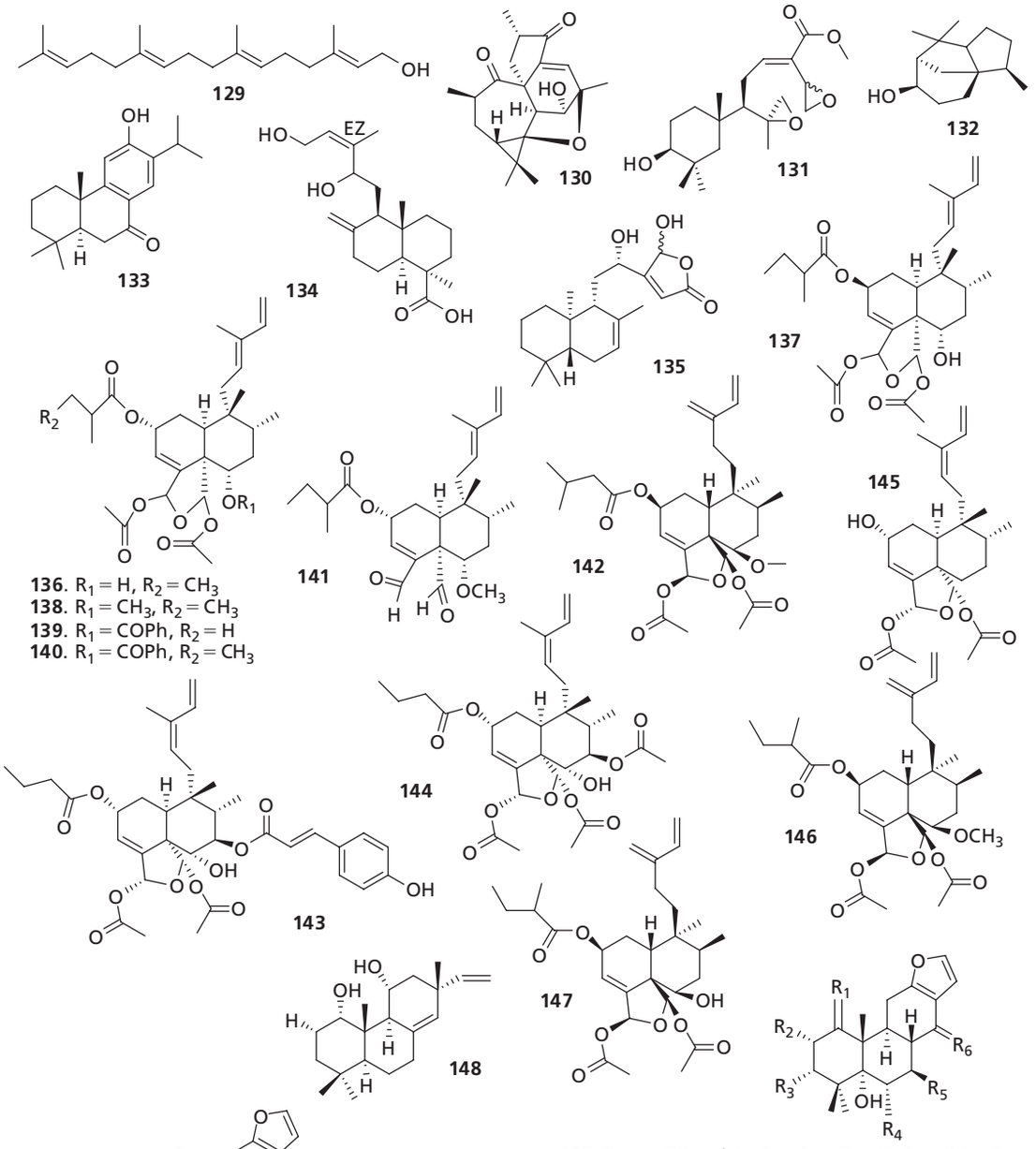



**Figure 10** Diterpenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*

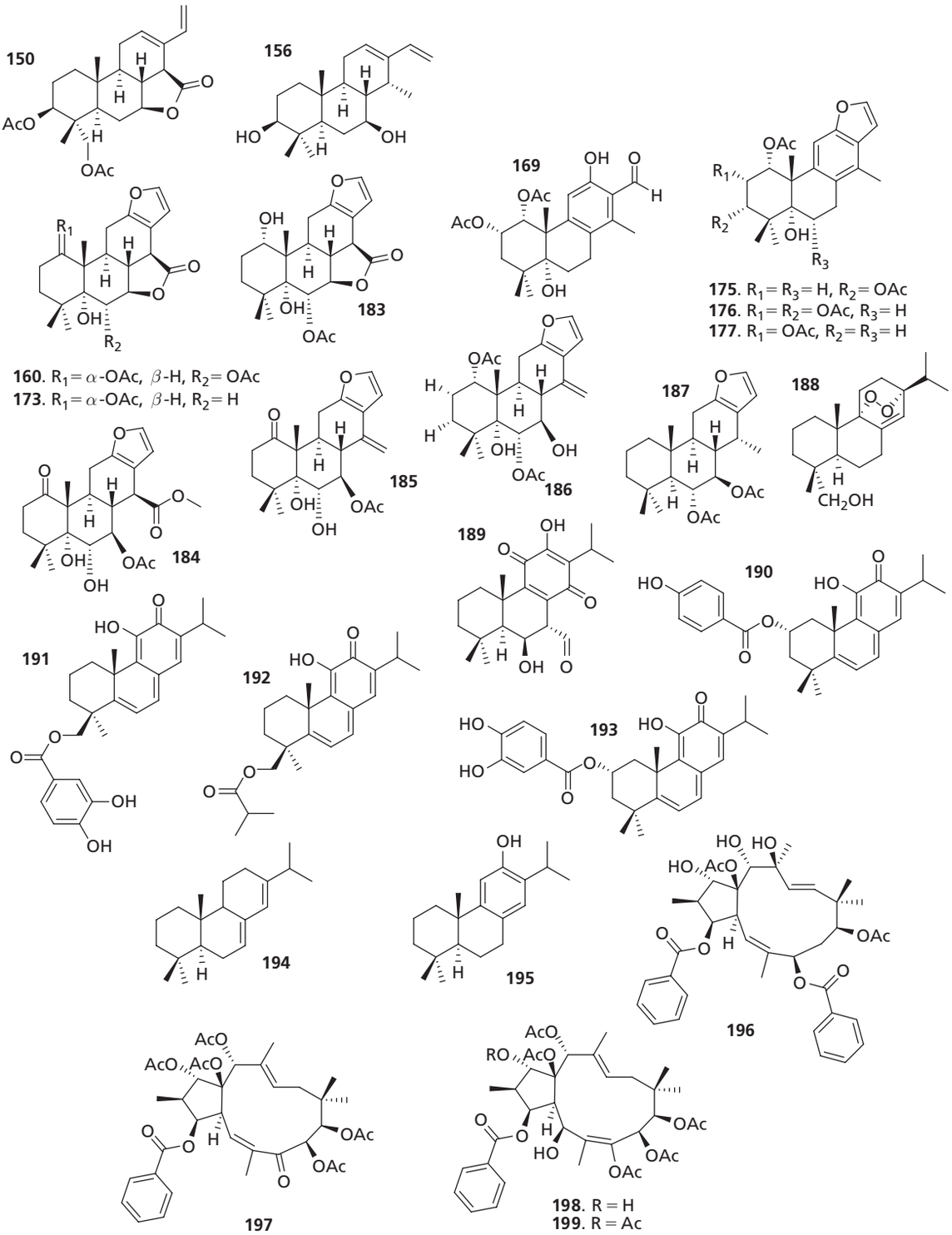



**Figure 10** (*Continued*)

## *Triterpenes*

From the stem bark of *Ekebergia capensis* Sparrm. (Meliaceae), a triterpenoid derivative was isolated and screened against FCR-3 and K1 strains. 2,3,22,23-Tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene (3*R*,22*R*) (**200**) displayed an IC50 of 18 $\mu$M and 7 $\mu$M on FCR-3 and K1, respectively, and showed *in vivo* parasitaemia suppression of 52.9% when given intraperitoneally.[105] Seven new and two known compounds were isolated from an ethyl acetate extract of the leaves of *Nuxia sphaerocephala*

Baker (Buddlejaceae) and have been considered moderately active, 3-oxolupenal (**201**) and 3$\beta$-hydroxy-lupenal (**202**) having the best activity with IC50 values of 3.6 and 7.2 $\mu$M, respectively, against FcB1.[106] One new and eight known ceanothane- and lupane-type triterpenes were isolated from the root bark of *Ziziphus cambodianus* Pierre (Rhamnaceae). The new compound, 3-*O*-vanillylceanothic acid (**203**), and two known compounds, 2-*O*-*E*-*p*-coumaroyl alphitolic acid (**204**) and zizyberenalic acid (**205**), exhibited notable antiplasmodial activity with IC50 values of 5.8, 1.5 and 6.6 $\mu$M, respectively.[107]

Bioassay-directed fractionation led to the isolation of betulinic acid 3-caffeate (**206**) from a sample of the dried leaves, twigs, and branches of *Diospyros quaesita* Thwaites (Ebenaceae). This compound showed strong antimalarial activity against D6 and W2 with IC50 values of 1.40 and 0.98 $\mu$M, respectively. Evaluation of **206** in the human oral epidermoid (KB) cancer cell line revealed cytotoxicity at an IC50 of 4.0 $\mu$M.[108] Phytochemical investigation of the $CH_2Cl_2$ extracts of *Erythrina stricta* Roxb. (Leguminosae) roots and *Erythrina subumbrans* Merr. (Leguminosae) stems led to the isolation of one triterpene, soyasapogenol B (**207**), which exhibited moderate antiplasmodial activity (10.0 $\mu$M) against K1.[18] Friedelan-3-one (**208**) was isolated from the root bark of *Harungana madagascariensis* Poir. (Clusiaceae). Its antiplasmodial activity was evaluated against W2 strain and gave an IC50 of 7.7 $\mu$M.[73] Garcinane (**209**) was isolated from the roots of *Garcinia polyantha* Oliv. (Clusiaceae) and exhibited antimalarial activity against NF54 with IC50 ranging from 2.5 to 4.1 $\mu$M.[35] A new bisnortriterpene quinone methide, 20-epi-isoiguesterinol (**211**) and a known compound, isoiguesterin (**210**), were isolated from the petroleum ether extract of the roots of *Salacia madagascariensis* DC. (Celastraceae). Compound **211** was active with IC50 of 0.16 $\mu$M on D6 and W2, and **210** with IC50 of 0.50 and 0.42 $\mu$M on D6 and W2, respectively.[109]

Bioassay-directed fractionation led to the isolation of 2$\alpha$,3$\beta$-dihydroxyolean-12-en-28-oic acid (**212**) from a sample of *Grewia bilamellata* Gagnep. (Tiliaceae), which displayed antimalarial activity against D6 and W2 (21.1 and 8.6 $\mu$M) without significant cytotoxicity.[41] A bioassay-guided fractionation from *Morinda lucida* Benth. (Rubiaceae) leaves and from *Satureja parvifolia* (Phil.) Epling (Lamiaceae) resulted in the isolation of two known triterpenic acids, ursolic acid (**213**) and oleanolic acid. These two compounds had already been evaluated *in vitro* but in these two studies some activity was observed for the first time, with IC50 of 32.3 and 19.8 $\mu$M for oleanolic acid, and 6.8 and 10.7 $\mu$M for ursolic acid. *In vivo*, oleanolic acid at a daily dose of 200 mg/kg produced 37.4% chemosuppression.[58,110] Bioactivity-guided fractionation of the petroleum ether extracts of the whole plants of *Viola verecunda* A. Gray (Violaceae) led to the isolation of epi-oleanolic acid (**214**), a triterpenoid, displaying high antiplasmodial activity against FcB1 strain (IC50 = 39 nM).[111]

Bioassay-guided fractionation of the antimalarial-active $CHCl_3$ extract of the dried stem of *Nauclea orientalis* (L.) L. (Rubiaceae) resulted in the isolation of a known compound, 3$\alpha$,23-dihydroxyurs-12-en-28-oic acid (**215**), which showed moderate activity with an IC50 of 9.7 $\mu$M on D6 and 12.7 $\mu$M on W2.[112] Three triterpenes were isolated from *Cogniauxia podolaena* Baill. (Cucurbitaceae), cucurbitacin B (**216**), cucurbitacin D (**217**) and 20-epibryonolic acid (**218**). All compounds obtained were assayed for antiplasmodial activity (on FcM29) and cytotoxicity. The IC50 values were 2.9, 7.8 and 3.7 $\mu$M, respectively. Both **216** and **217** have high cytotoxicity, whereas **218** showed a better selectivity index.[113] A compound was isolated from the active fraction of *Salvia radula* Epling (Lamiaceae) and identified as betulafolientriol oxide (**219**). It displayed moderate antimalarial activity (IC50 = 10.4 $\mu$M).[114]

A quassinoid, neosergeolide (**220**), isolated from the roots and stems of *Picrolemma sprucei* Hook.f. (Simaroubaceae), possessed a significant inhibitory effect (more active than quinine and chloroquine) on K1 strain (IC50 = 2 nM).[49] Two new limonoids, domesticulide B (**221**) and C (**222**), and three more known ones, methyl 6-acetoxyangolensate (**223**), azadiradione (**224**) and dukunolide C (**225**), were isolated from seeds of *Lansium domesticum* Corrêa (Meliaceae) and showed antimalarial activity against K1 with IC50 values of 6.0, 4.1, 7.2, 6.4, 9.6 $\mu$M, respectively.[115] Marked antimalarial activity was observed for anthothecol (**226**), a limonoid of *Khaya anthotheca* C.DC. (Meliaceae). IC50 values were 1.4 and 0.17 $\mu$M against W2 strain using two different assays.[116] In the search for active principles from the stem bark of *Entandrophragma angolense* C.DC. (Meliaceae), 7$\alpha$-obacunyl acetate (**227**) was isolated and tested against W2 strain. It exhibited antimalarial activity with an IC50 of 4.0 $\mu$M.[117] Two limonoids isolated from the seeds of *Chisocheton siamensis* Craib (Meliaceae) were tested for antimalarial activity. Dysobinin (**228**) and mahonin (**229**) showed an inhibitory effect against K1 with IC50 values of 4.2 and 5.7 $\mu$M, respectively.[118] The dicholoromethane extract of *Pseudocedrela kotschyi* Harms (Meliaceae) root commonly used in Malian traditional medicine led to the isolation of two known compounds, 7-deacetylgedunin (**230**) and 7-deacetyl-7-oxogedunin (**231**), which exhibited activity against K1 (IC50 = 3.1 and 4.1 $\mu$M, respectively).[119] Compound **231** was also isolated from the stem bark of *Ekebergia capensis* Sparrm. (Meliaceae) and screened against FCR-3 strain with an IC50 of 6 $\mu$M.[105]

Figure 11 shows triterpenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### Steroids

Four new pregnane glycosides, 12-*O*-benzoyl-20-*O*-acetyl 3$\beta$,12$\beta$,14$\beta$,20$\beta$-tetrahydroxy-(20*S*)-pregn-5-ene-6-deoxy-3-*O*-methyl-$\beta$-D-allopyranosyl(1→4)-$\beta$-D-cymaropyranosyl (1→4)-$\beta$-D-cymaropyranoside (**232**), 12-*O*-benzoyl-20-*O*-acetyl 3$\beta$,7$\alpha$,12$\beta$,14$\beta$,20$\beta$-tetrahydroxy-(20*S*)-pregn-5-ene-6-deoxy-3-*O*-methyl-$\beta$-D-allopyranosyl-(1→4)-$\beta$-D-cymaropyranosyl-(1→4)-$\beta$-D-cymaropyranoside (**233**), 12-*O*-benzoyl-20-*O*-acetyl 3$\beta$,5$\alpha$,12$\beta$,14$\beta$,20$\beta$-pentahydroxy-(20*S*)-pregn-6-ene-$\beta$-D-glucopyranosyl-(1→4)-6-deoxy-3-*O*-methyl-$\beta$-D-allopyranosyl-(1→4)-$\beta$-D-cymaropyranosyl-(1→4)-$\beta$-D-cymaropyranoside (**234**) and 12,20-dibenzoyl-3$\beta$,12$\beta$,14$\beta$,20$\beta$-tetrahydroxy-(20*S*)-pregn-5-ene-$\beta$-D-glucopyranosyl-(1→4)-6-deoxy-3-*O*-methyl-$\beta$-D-allopyranosyl-(1→4)-$\beta$-D-cymaropyranosyl-(1→4)-$\beta$-D-cymaropyranoside

(**235**) were isolated from *Caralluma tuberculata* N.E.Br. (Asclepiadaceae), in addition to a known one, russelioside E (**236**). All the isolated compounds were tested for their antimalarial activity against K1 and had IC50 = 7.4, 6.5, 9.6, 5.7 and 7.5 $\mu$M, respectively.[120]

Figure 12 shows steroids with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

Table 3 gives the tested terpenoid compounds presenting low or no activity *in vitro* against various strains of *P. falciparum*.[41,58,65,74,78,80,87,89,92,94,105,110,115,117–119,121–140]

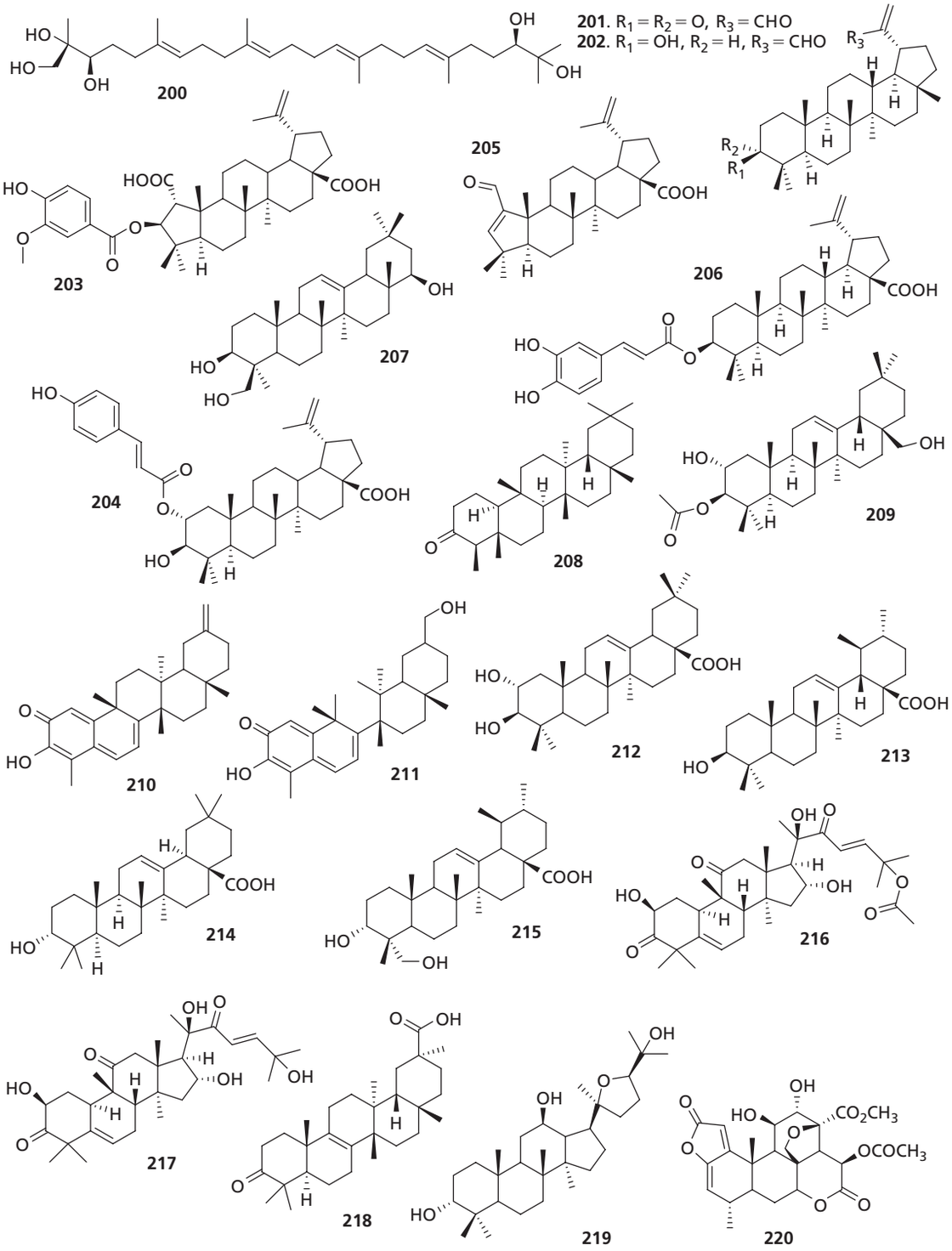



**Figure 11** Triterpenes with moderate or promising activity *in vitro* against various strains of *P. falciparum*

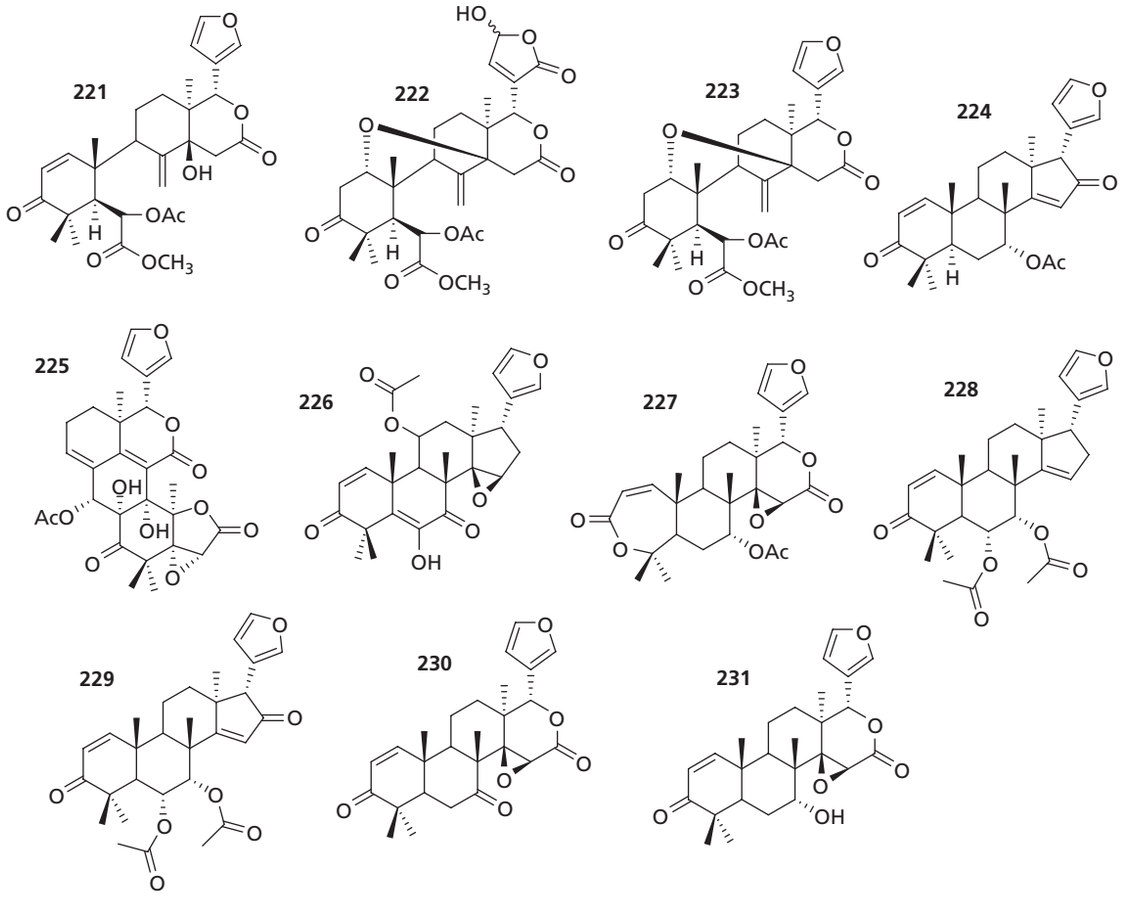
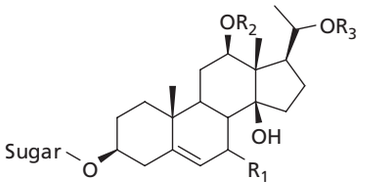
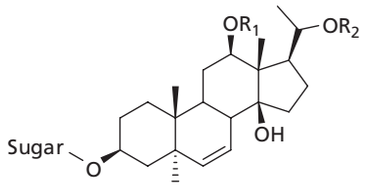


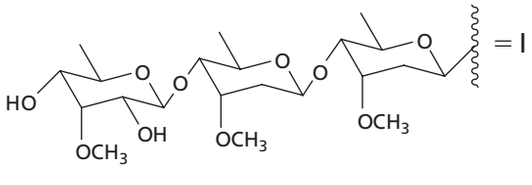

**Figure 11** (*Continued*)



**232**. $R_1$ = H, $R_2$ = Benzoyl, $R_3$ = Acetyl, Sugar = I
**233**. $R_1$ = OH, $R_2$ = Benzoyl, $R_3$ = Acetyl, Sugar = I
**235**. $R_1$ = H, $R_2$ = $R_3$ = Benzoyl, Sugar = II
**236**. $R_1$ = H, $R_2$ = Benzoyl, $R_3$ = Acetyl, Sugar = II



**234**. $R_1$ = Benzoyl, $R_2$ = Acetyl, Sugar = II



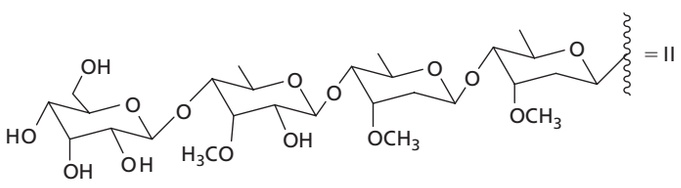


**Figure 12** Steroids with moderate or promising activity *in vitro* against various strains of *P. falciparum*

## Alkaloids

### *Ornithine and lysine derivatives*

The methanolic extract of *Albizia gummifera* C.A.Sm. (Leguminosae) was fractionated to isolate five known spermine alkaloids from the alkaloidal fraction, budmunchiamine K (**237**), 6-hydroxybudmunchiamine K (**238**), 5-normethylbudmunchiamine K (**239**), 6-hydroxy-5-normethylbudmunchiamine K (**240**) and 9-normethylbudmunchiamine K (**241**). These alkaloids exhibited good activity with IC50 values of 0.18, 0.29, 0.20, 0.33

**Table 3** Terpenoid compounds presenting low or no activity *in vitro* against various strains of *P. falciparum*

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| 16-Hydroxycleroda-3,13(14)*Z*-dien-15,16-olide | *Goniothalamus marcanii* Craib | Annonaceae | 11.3 (K1) | 74 |
| Lupeol | *Holarrhena floribunda* T.Durand & Schinz | Apocynaceae | >50 (FCR-3/3D7) | 121 |
| 3-*O*-(3′-Hydroxyeicosanoyl)lupeol | *Holarrhena floribunda* T.Durand & Schinz | Apocynaceae | >50 (FCR-3/3D7) | 121 |
| 3-*O*-[(2′-(Tetracosyloxy)acetyl]lupeol | *Holarrhena floribunda* T.Durand & Schinz | Apocynaceae | >50 (FCR-3/3D7) | 121 |
| 3-*O*-[(1″-Hydroxyoctadecyloxy)-2′-hydroxypropanoyl]lupeol | *Holarrhena floribunda* T.Durand & Schinz | Apocynaceae | >50 (FCR-3/3D7) | 121 |
| Uzarigenin | *Calotropis gigantean* (L.) W.T.Aiton | Asclepiadaceae | >50 (K1) | 122 |
| Calactin | *Calotropis gigantean* (L.) W.T.Aiton | Asclepiadaceae | >50 (K1) | 122 |
| Calotropin | *Calotropis gigantean* (L.) W.T.Aiton | Asclepiadaceae | >50 (K1) | 122 |
| Taraxasteryl acetate | *Calotropis gigantean* (L.) W.T.Aiton | Asclepiadaceae | >50 (K1) | 122 |
| Esacetyl-$\alpha$-cyclopyrethrosin | *Oncosiphon piluliferum* (L.f.) Källersjö | Asteraceae | 16.7 (D10) | 78 |
| 1,10-Dioxo-1,10-deoxy-1,10-secogorgonolide | *Artemisia gorgonum* Webb | Asteraceae | 50.0 (FcB1) | 80 |
| 3$\beta$,4$\beta$-Epoxy-1$\beta$,10$\beta$-epiarborescin | *Artemisia gorgonum* Webb | Asteraceae | 50.4 (FcB1) | 80 |
| Arborescin | *Artemisia gorgonum* Webb | Asteraceae | 15.3 (FcB1) | 80 |
| 1$\beta$,10$\beta$-Epoxy-2$\alpha$-hydroxykauniolide | *Artemisia gorgonum* Webb | Asteraceae | 22.1 (FcB1) | 80 |
| 1$\alpha$,4$\alpha$,10$\alpha$-Trihydroxy-5$\alpha$,11$\beta$H-guaia-2-en-12,6$\alpha$-olide | *Artemisia gorgonum* Webb | Asteraceae | 32.1 (FcB1) | 80 |
| Ridentin | *Artemisia gorgonum* Webb | Asteraceae | 21.4 (FcB1) | 80 |
| Anthecularin | *Anthemis auriculata* Boiss. | Asteraceae | >50 (K1) | 123 |
| Anthecotulide | *Anthemis auriculata* Boiss. | Asteraceae | 16.1 (K1) | 87 |
| 4-Acetoxyanthecotulide | *Anthemis auriculata* Boiss. | Asteraceae | 16.7 (K1) | 87 |
| Methyl populnoate | *Austroplenckia populnea* (Reissek) Lundell | Celastraceae | >50 (D6) | 124 |
| Populnoic acid | *Austroplenckia populnea* (Reissek) Lundell | Celastraceae | >50 (D6) | 124 |
| Stigmast-5-en-3-*O*-$\beta$-(D-glucopyranoside) | *Austroplenckia populnea* (Reissek) Lundell | Celastraceae | >50 (D6) | 124 |
| Endodesmiadiol | *Endodesmia calophylloides* Benth. | Clusiaceae | 13.0 (W2) | 125 |
| Canophyllal | *Endodesmia calophylloides* Benth. | Clusiaceae | 18.2 (W2) | 125 |
| Cerin | *Endodesmia calophylloides* Benth. | Clusiaceae | 14.1 (W2) | 125 |
| Morelloflavone | *Endodesmia calophylloides* Benth. | Clusiaceae | 23.6 (W2) | 125 |
| 3$\beta$-Acetoxyoleanolic acid | *Endodesmia calophylloides* Benth. | Clusiaceae | 13.1 (W2) | 125 |
| Sutherlandioside A | *Sutherlandia frutescens* (L.) R. Br. | Fabaceae | >50 (D6/W2) | 126 |
| Sutherlandioside B | *Sutherlandia frutescens* (L.) R. Br. | Fabaceae | >50 (D6/W2) | 126 |
| Sutherlandioside C | *Sutherlandia frutescens* (L.) R. Br. | Fabaceae | >50 (D6/W2) | 126 |
| Sutherlandioside D | *Sutherlandia frutescens* (L.) R. Br. | Fabaceae | >50 (D6/W2) | 126 |
| Laetianolide A | *Laetia procera* (Poepp.) Eichler | Flacourtiaceae | 57.6 (F32)<br>27.5 (FCb1) | 92 |
| 15-*O*-Ethylleopersin C | *Leonurus cardiaca* L. | Lamiaceae | >50 (D6/W2) | 127 |
| 15-*O*-Methylleopersin C | *Leonurus cardiaca* L. | Lamiaceae | >50 (D6/W2) | 127 |
| 15-Epi-*O*-methylleopersin C | *Leonurus cardiaca* L. | Lamiaceae | >50 (D6/W2) | 127 |
| 12,17-Diacetoxy,15-hydroxy,2-oxo,3,13 *E*(14)-diene clerodane | *Gomphostemma crinitum* Wall. | Lamiaceae | 22.14 (MRC-02) | 128 |
| Fagraldehyde | *Fagraea fragrans* Roxb. | Loganiaceae | >50 (W2) | 129 |
| Geranylfarnesol | *Thalia geniculata* L. | Marantaceae | 12.7 | 130 |
| Kurubasch aldehyde | *Trichilia emetica* Vahl. | Meliaceae | 76 (3D7) | 131 |
| 16-Oxolabda-8(17),12(*E*)-dien-15-oic acid | *Turraeanthus africana* Pellegr. | Meliaceae | 83.1 (F32) | 132 |
| Methyl 14,15-epoxylabda-8(17),12*E*-diene-16-oate | *Turraeanthus africana* Pellegr. | Meliaceae | >50 (F32) | 133 |
| Ekeberin D4 | *Ekebergia capensis* Sparrm. | Meliaceae | 40 (FCR-3) | 105 |
| Domesticulide D | *Lansium domesticum* Corrêa | Meliaceae | 11.8 (K1) | 115 |
| 6-Acetoxymexicanolide | *Lansium domesticum* Corrêa | Meliaceae | 18.4 (K1) | 115 |
| Walsuronoid | *Walsura robusta* Roxb. | Meliaceae | 40% at 40 $\mu$M (3D7) | 134 |
| Walsuronoid B | *Walsura robusta* Roxb. | Meliaceae | 40% at 40 $\mu$M (3D7) | 134 |
| 24-Methylene cycloartenol | *Entandrophragma angolense* C.DC. | Meliaceae | 12.3 (W2) | 117 |
| 7$\alpha$-Acetoxydihydronomilin | *Entandrophragma angolense* C.DC. | Meliaceae | 34.9 (W2) | 117 |
| Methylangolensate | *Entandrophragma angolense* C.DC. | Meliaceae | 48.7 (W2) | 117 |
| 6$\alpha$-Acetoxyepoxyazadiradione | *Chisocheton siamensis* Craib | Meliaceae | 12.0 (K1) | 118 |
| Kotschyin A | *Pseudocedrela kotschyi* Harms | Meliaceae | > 5 (K1) | 119 |
| Methyl 3,4-dihydroxy-5-(3-methyl-2-butenyl)benzoate | *Piper glabratum* Kunth | Piperaceae | 17.4 (F32) | 135 |
| Methyl 4-hydroxy-3-(3-methyl-2-butenyl)benzoate | *Piper glabratum* Kunth | Piperaceae | 12.7 (F32) | 135 |

(*Continued*)

**Table 3** (*Continued*)

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| Benzoic acid,3-[2-(acetyloxy)-3-methyl-3-buten-1-yl]-4,5-dihydroxy-,methyl ester | *Piper glabratum* Kunth | Piperaceae | 34.0 (F32) | 135 |
| 3-(*Z*)-Caffeoyllupeol | *Bruguiera parviflora* Wight | Rhizophoraceae | 14.6 (K1) | 136 |
| Oleanolic acid | *Morinda lucida* Benth. | Rubiaceae | 32.3 (CQs) | 110 |
| | *Satureja parvifolia* (Phil.) Epling | Lamiaceae | 19.8 (3D7) | 58 |
| $\beta$-Acetylolean-12-en-28-olic acid | *Prismatomeris fragrans* Geddes | Rubiaceae | 11.9 (K1) | 137 |
| Methyl uguenenoate | *Vepris uguenensis* Engl. | Rutaceae | 20.7 (3D7)<br>27.5 (FCM29) | 65 |
| 3,4-Dihydro-methylcatalpol | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| Scrolepidoside | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| Catalpol | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| 6-*O*-Methylcatalpol | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| Sinuatol | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| aucubin | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| 6-*O*-$\beta$-D-Xylopyranosylaucubin | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| Ajugol | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| Ajugoside | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| Iridoid-related aglycone | *Scrophularia lepidota* Boiss. | Scrophulariaceae | >50 (K1) | 138 |
| 3-*O*-$\beta$-D-glucopyranosylpseudojujubogenin | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacoside A3 | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacoside A6 | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopaside II | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopaside IV | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopaside V | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopaside X | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopaside N2 | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopasaponin C | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Bacopasaponin G | *Bacopa monniera* Wettst | Scrophulariaceae | >50 | 139 |
| Buddlejasaponin | *Scrophularia cryptophilla* Boiss. & Heldr. | Scrophulariaceae | 24.5 (K1) | 140 |
| 3$\alpha$,20-Lupandiol | *Grewia bilamellata* Gagnep. | Tiliaceae | 19.8 (D6)<br>19.1 (W2) | 41 |
| Aulacocarpin A | *Aframomum zambesiacum* K. Schum | Zingiberaceae | 13.7 (FcB1) | 89 |
| Zambesiacolactone A | *Aframomum zambesiacum* K. Schum | Zingiberaceae | 17.2 (FcB1) | 89 |
| Zambesiacolactone B | *Aframomum zambesiacum* K. Schum | Zingiberaceae | 15.5 (FcB1) | 89 |
| (1*R*,2*S*,5*S*,9*S*,10*S*,11*R*,13*R*)-1,2,11-trihydroxypimara-8(14),15-diene | *Kaempferia marginata* Carey | Zingiberaceae | 27.5 (K1) | 94 |

and 0.24 $\mu$M, respectively, on NF54, and 1.43, 1.73, 1.88, 1.72 and 1.79, respectively, on ENT30. Four of these alkaloids were further evaluated intraperitoneally for activity against *P. berghei in vivo*. The alkaloids showed chemosuppression percentages of parasitaemia in mice ranging from 43 to 72% at 20 mg/kg per day The use of the extracts of *A. gummifera* for the treatment of malaria in traditional medicine seems to have a scientific basis.[141] Vertine (**242**) and epi-lyfoline (**243**) were isolated from *Heimia salicifolia* Link & Otto (Lythraceae) and showed antimalarial activity with IC50 values of 10.9 and 6.7 $\mu$M, respectively.[142] A new lycorine derivative LT1 (**244**), 1-*O*-(30*S*)-hydroxybutanoyllycorine was isolated from the aerial part and bulbs of *Lycoris traubii* Hayward (Amaryllidaceae). It showed significant activity against FCR-3 and K1 strains (IC50 = 1.2 and 1.6 $\mu$M, respectively).[143]

Figure 13 shows alkaloids derived from ornithine and lysine with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### Phenylalanine and tyrosine derivatives

A novel alkaloid with an unprecedented tricyclic skeleton, cassiarin A (**245**), was isolated from the leaves of *Cassia siamea* Lam. (Leguminosae). It showed promising antiplasmodial activity (IC50 23.5 nM).[144] *Zanthoxylum rhoifolium* Lam. (Rutaceae) bark is a medicinal plant traditionally used in French Guiana to treat and prevent malaria. Bioassay-guided fractionation of the alkaloid extract yielded three benzophenanthridine alkaloids. Dihydronitidine (**246**) was evaluated against FcB1 (IC50 = 4.9 $\mu$M).[145] Biologically guided fractionation of the methanolic extract of the roots of *Zanthoxylum flavum* Vahl (Rutaceae) led to the isolation of two alkaloids, dihydrochelerythrin (**247**) and chelerythrine acetonate (**248**). Compound **247** was only moderately active with an IC50 of 10.6 $\mu$M on D6. Compound **248** displayed greater activity with IC50 values of 5.7 and 3.4 $\mu$M on D6 and W2 strains, respectively.[40] Decoction of *Strychnopsis thouarsii* Baill. (Menispermaceae) is used in Malagasy traditional medicine to fight malaria. It has been shown that this traditional remedy prevents malaria infection by targeting *Plasmodium* at its early liver stage. Bioassay-guided fractionation of *S. thouarsii* stem barks extracts, using a rodent *Plasmodium yoelii* liver stage parasites inhibition assay, led to the isolation the new morphinan alkaloid tazopsine (**249**) together with sinococuline (**250**).

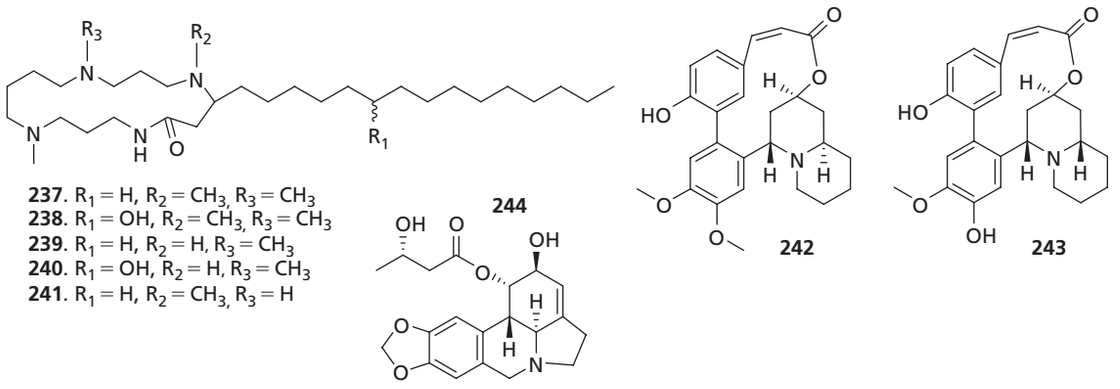



**Figure 13** Alkaloids derived from ornithine and lysine with moderate or promising activity *in vitro* against various strains of *P. falciparum*

Compounds **249** and **250** exhibited selective inhibitory activity (SI > 13.8) against *P. yoelii* liver stage *in vitro*. Tazopsine showed the most potent inhibitory activity with an IC50 value of 3.1 $\mu$M. Sinococuline was both slightly less active (IC50 = 4.5 $\mu$M) and less toxic.[146,147] Dehydroroemerine (**251**) was isolated from *Stephania rotunda* Lour. (Menispermaceae) and was found to be the most active against W2 with an IC50 value of 0.36 $\mu$M.[148] Two new alkaloids, desmorostratine (**252**) and discretine *N*-oxide (**253**), were isolated from the stem bark of *Desmos rostrata* (Merr. & Chun) P.T.Li (Annonaceae), together with five known alkaloids including discretine (**254**) and dehydrodiscretine (**255**). Compounds **253**, **254** and **255** inhibited FcB1 with IC50 values of 4.2, 1.6 and 0.9 $\mu$M, respectively, and showed weak cytotoxic activity. On the other hand, **252** had an IC50 of 3.6 $\mu$M but was also moderately toxic (IC50 = 2.4 $\mu$M).[149] A new dimeric aporphine alkaloid, bidebiline E (**256**), was isolated from the roots of *Polyalthia cerasoides* (Roxb.) Bedd. (Annonaceae). It exhibited antimalarial activity against K1 (IC50 = 7.7 $\mu$M).[150] Three alkaloids, melosmine (**257**), atherospermidine (**258**) and isomoschatoline (**259**), isolated from the ethyl acetate extract of the stem of *Rollinia pittieri* Saff. and *Pseudomalmea boyacana* (J.F. Macbr.) Chatrou (Annonaceae) exhibited moderate activity with IC50 values of 12.2, 10.6 and 10.9 $\mu$M, respectively, against F32, and 10.4, 12.8 and 27.8 $\mu$M against W2.[151] Two bioactive bisbenzylisoquinolines, magnoline (**260**) and magnolamine (**261**), were isolated from the leaves of *Michelia figo* (Lour.) Sprenge (Magnioliaceae). Magnolamine showed a significant IC50 of 1.28 $\mu$M on K1 and less than 0.16 $\mu$M on FCR3. Magnoline also inhibited both strains with an IC50 of 1.51 $\mu$M on FCR3 and less than 0.16 $\mu$M on K1.[152] A new diastereoisomer of the bis-benzylisoquinoline alkaloid rodiasine, 1*S*,1′*R*-rodiasine (**262**), was isolated from *Pseudoxandra cuspidata* Maas (Annonaceae) bark, used in French Guiana as an antimalarial. The antimalarial activity of this bark was mostly due to **262** (IC50 = 1.14 $\mu$M), which also displayed low cytotoxicity.[153] The antiplasmodial activity of *Triclisia sacleuxii* Diels (Menispermaceae) was investigated on 3D7 and W2 strains. Phytochemical analysis of the root tertiary alkaloids fraction yielded four major compounds, phaeanthine (**263**), *N*-methylapateline (**264**), 1,2-dehydroapateline (**265**) and 1,2-dehydrotelobine (**266**). They demonstrated antiplasmodial activity with IC50 values of 1.72, 0.93, 1.39 and 12.4 $\mu$M, respectively, on 3D7, and 0.35, 1.10, 1.63 and 1.52 $\mu$M, respectively, on W2.[154] Three new fully dehydrogenated naphthylisoquinoline alkaloids, the 7,1′-coupled *ent*-dioncophylleine A (**267**), the 7,1′-coupled 5′-*O*-demethyl-*ent*-dioncophylleine A (**268**), and the 7,8′-linked dioncophylleine D (**269**), were isolated from the leaves of the liana *Ancistrocladus benomensis* Rischer & G.Bringmann (Ancistrocladaceae). Compounds **267** and **268** exhibited moderate antiplasmodial activity against K1 with IC50 values of 10.5 and 8.6 $\mu$M, respectively. Compound **269** showed better activity with a low IC50 (1.3 $\mu$M).[155] From the roots of a recently discovered *Ancistrocladus* taxon with close affinity to *Ancistrocladus congolensis* J. Léonard (Ancistrocladaceae), six new naphthylisoquinoline alkaloids, 5′-*O*-demethylhamatine (**270**), 5′-*O*-demethylhamatinine (**271**), 6-*O*-demethylancistroealaine A (**272**), 6,5′-*O*,*O*-didemethylancistroealaine A (**273**), 5-epi-6-*O*-methylancistrobertsonine A (**274**), and 5-epi-4′-*O*-demethylancistrobertsonine C (**275**), and also the known 6-*O*-demethylancistrobrevine A (**276**), were isolated. All of the naphthylisoquinoline alkaloids tested were found to exhibit antiplasmodial activity against K1 strain: IC50 = 2.5, 7.2, 4.4, 5.4, 4.4, 6.2 and 5.0 $\mu$M, respectively.[156]

Figure 14 shows alkaloids derived from phenylalanine and tyrosine with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

### *Tryptophane derivatives*

Bioassay-guided fractionation of the antimalarial $CHCl_3$ extract of the dried stem of *Nauclea orientalis* (L.) L. (Rubiaceae) resulted in the isolation of a novel tetrahydro-$\beta$-carboline monoterpene alkaloid glucoside, naucleaorine (**277**), which showed activity with an IC50 of 6.9 $\mu$M on D6 and 8.0 on W2.[112] An indole alkaloid, naucleofficine A (**278**), was isolated from the stems (with bark) of *Nauclea officinalis* Pierre ex Pitard (Rubiaceae). Compound **278** exhibited moderate antimalarial activity against FCC1-HN with an IC50 value of 9.7 $\mu$M and no cytotoxic effect was observed.[157] A dimeric indoloquinoline alkaloid, biscryptolepine (**279**), originally obtained from the plant *Cryptolepis sanguinolenta* (Lindl.) Schltr. (Asclepiadaceae), showed

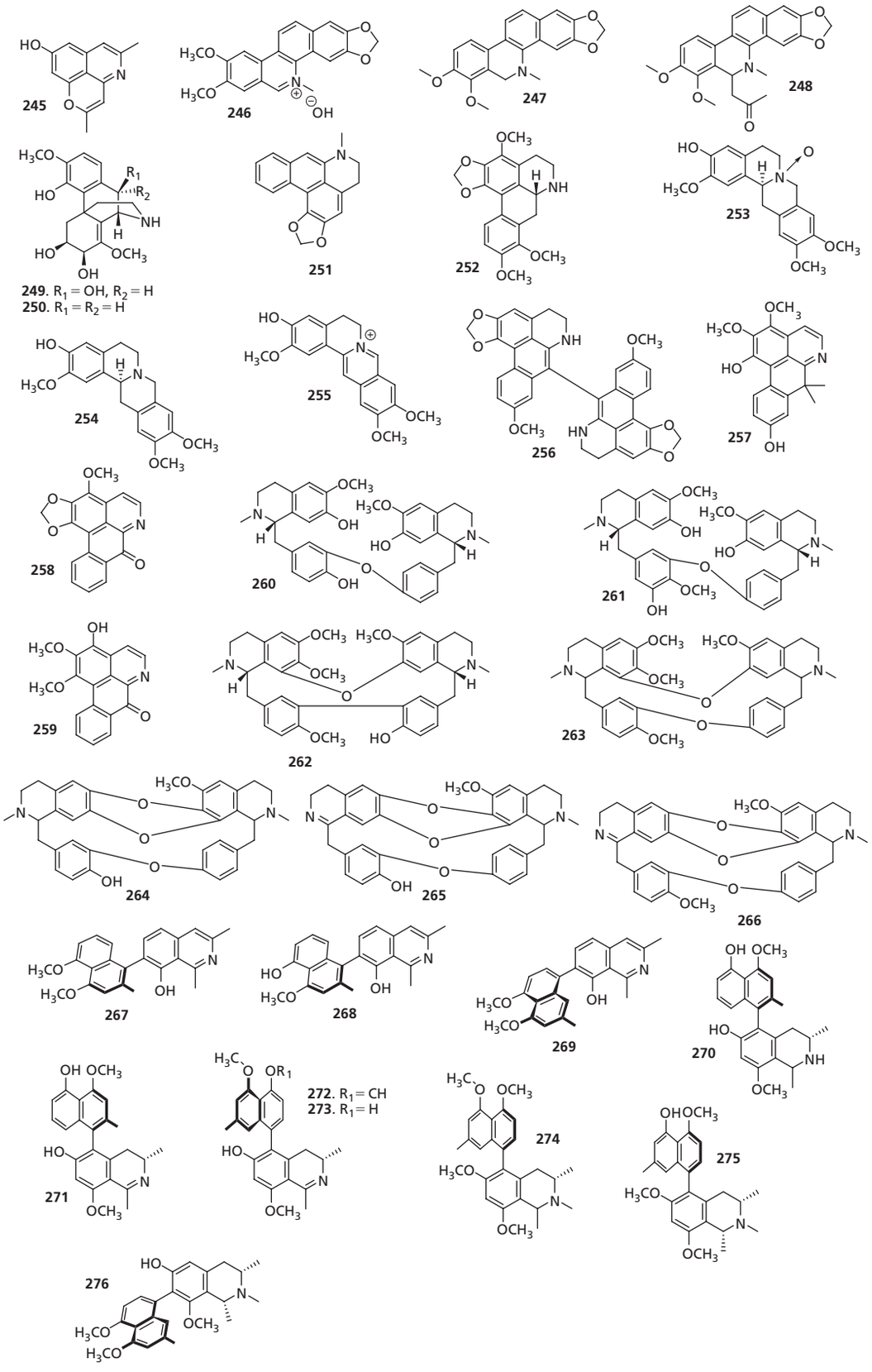



**Figure 14** Alkaloids derived from phenylalanine and tyrosine with moderate or promising activity *in vitro* against various strains of *P. falciparum*

good antiplasmodial activity against K1 (IC50 of 0.27 $\mu$M), while the cytotoxicity (L6 cells) was 13.62 $\mu$M.[158] Biologically guided fractionation of the methanolic extract of the roots of *Zanthoxylum flavum* Vahl (Rutaceae) led to the isolation of dihydrorutaecarpine (**280**) which displayed higher activity with IC50 values of 5.7 and 3.4 $\mu$M on D6 and W2 strains, respectively.[40] Isosungucine is a quasi-symmetric bisindolomonoterpenoid alkaloid isolated from the roots of *Strychnos icaja* Baill. (Loganiaceae). The antimalarial activity against the *P. vinckei petteri* murine strain was determined *in vivo*. In the Peters 4-day suppressive test, the compound suppressed parasitaemia by almost 50% on day 4 at a dose of 30 mg/kg given intraperitoneally.[159]

Figure 15 shows alkaloids derived from tryptophane with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

## Steroidal alkaloids

Bioguided phytochemical investigation of *Sarcococca hookeriana* Baill. (Buxaceae) yielded two new pregnane-type steroidal alkaloids hookerianamide H (**281**) and hookerianamide I (**282**), along with three known alkaloids, Na-methylepipachysamine D (**283**), sarcovagine C (**284**) and dictyophlebine (**285**). These compounds showed reasonable antiplasmodial activity with IC50 values of 3.5, 6.6, 10.3, 3.4 and 2.4, respectively, against W2 strain.[160] Bioassay-guided fractionation of the EtOH extract of the stem bark of *Funtumia elastica* Stapf (Apocynaceae) resulted in the isolation of four steroidal alkaloids, holarrhetine (**286**), conessine (**287**), holarrhesine (**288**) and isoconessimine (**289**). They exhibited antiplasmodial activity against FcB1 strain with IC50 values of 1.13, 1.04, 0.97 and 3.39 $\mu$M and weak cytotoxicity (L-6 cell line) with IC50 values of 5.13, 14.6, 7.49 and 36.55 $\mu$M.[161]

Figure 16 shows steroidal alkaloids with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

## Other N-containing compounds

Bioassay-guided fractionation of the EtOAc extract of the roots of Thai *Ziziphus oenoplia* L. Mill. var. *brunoniana* (Rhamnaceae) resulted in the isolation of two new 13-membered cyclopeptide alkaloids of the 5(13) type, ziziphine N (**290**) and Q (**291**), which exhibited notable antiplasmodial activity with IC50 values of 6.4 and 5.9 $\mu$M, respectively.[162] Three alkamides were isolated from the leaves of *Zanthoxylum syncarpum* Tul. (Rutaceae). Compound **292**, the racemic form of the known compound syncarpamide, showed moderate antiplasmodial activity, with IC50 values of 4.2 and 6.1 $\mu$M against D6 and W2 clones, respectively. Cytotoxicity was evaluated at an IC50 of 10.3 $\mu$M.[163]

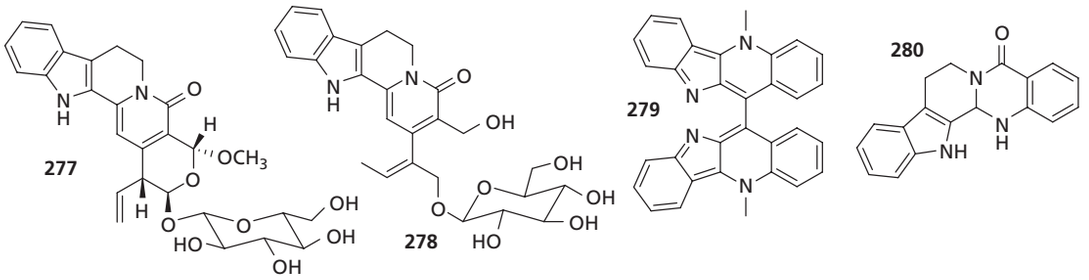



**Figure 15** Alkaloids derived from tryptophane with moderate or promising activity *in vitro* against various strains of *P. falciparum*

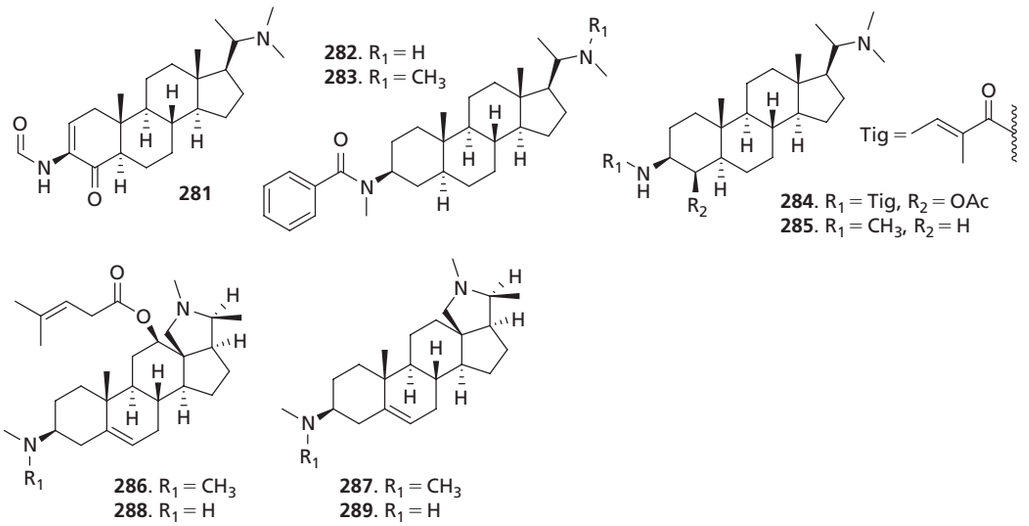
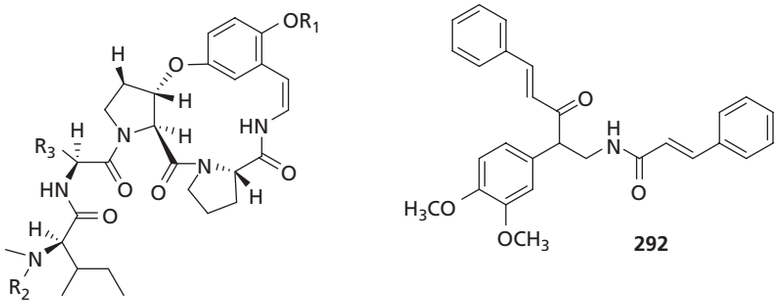



**Figure 16** Steroidal alkaloids with moderate or promising activity *in vitro* against various strains of *P. falciparum*




**290**. $R_1 = R_2 = CH_3$, $R_3 = CH_2CH(CH3)_2$
**291**. $R_1 = R_2 = CH_3$, $R_3 = CH(CH_3)_2$

**Figure 17** Other *N*-containing compounds with moderate or promising activity *in vitro* against various strains of *P. falciparum*

**Table 4** Alkaloids presenting low or no activity *in vitro* against various strains of *P. falciparum*

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| Predicentrine | *Desmos rostrata* (Merr. & Chun) P.T.Li | Annonaceae | 27.8 (FcB1) | 149 |
| Aristolactam | *Desmos rostrata* (Merr. & Chun) P.T.Li | Annonaceae | >37 (FcB1) | 149 |
| Octadeca-9,11,13-triynoic acid | *Polyalthia cerasoides* (Roxb.) Bedd. | Annonaceae | 18.4 (K1) | 150 |
| N-methylouregidione | *Pseuduvaria setosa* (King) J. Sinclair. | Annonaceae | >50 (K1) | 164 |
| Ouregidione | *Pseuduvaria setosa* (King) J. Sinclair. | Annonaceae | >50 (K1) | 164 |
| Oxostephanine | *Pseuduvaria setosa* (King) J. Sinclair. | Annonaceae | >50 (K1) | 164 |
| Ellipticine | *Aspidosperma vargasii* A.DC. *Aspidosperma desmanthum* Benth. | Apocynaceae | >50 (K1) | 49 |
| Aspidocarpine | *Aspidosperma vargasii* A.DC. *Aspidosperma desmanthum* Benth. | Apocynaceae | 19 (K1) | 49 |
| Integerrimide A | *Jatropha integerrima* Jacq. | Euphorbiaceae | >50 (K1) | 165 |
| Integerrimide A | *Jatropha integerrima* Jacq. | Euphorbiaceae | >50 (K1) | 165 |
| (–)-Phoebescortechiniine | *Phoebe scortechinii* (Gamb.) Kochummen | Lauraceae | Nt | 166 |
| Phoebegrandine A | *Phoebe scortechinii* (Gamb.) Kochummen | Lauraceae | Alkaloidal extract = | 166 |
| Phoebegrandine B | *Phoebe scortechinii* (Gamb.) Kochummen | Lauraceae | 6.11 g/ml (Gombak A) | 166 |
| Tetrahydropronuciferine | *Phoebe scortechinii* (Gamb.) Kochummen | Lauraceae | 0.69 g/ml (D10) | 166 |
| Cassiarin B | Cassia siamea Lam. | Leguminosae | 22.0 | 144 |
| 10-Epi-tazopsine | *Strychnopsis thouarsii* Baill. | Menispermaceae | 16.1 (*P. yoelii*) | 147 |
| Tetrahydropalmatine | *Stephania rotunda* Lour. | Menispermaceae | 32.6 (W2) | 148 |
| Xylopinine | *Stephania rotunda* Lour. | Menispermaceae | >50 (W2) | 148 |
| Cycleanine *N*-oxide | *Epinetrum villosum* (Exell) Troupin | Menispermaceae | 13.5 (FcB1) | 167 |
| Epimethoxynaucleaorine | *Nauclea orientalis* (L.) L. | Rubiaceae | 12.4 (D6)<br>13.2 (W2) | 112 |
| Naucleofficine B | *Nauclea officinalis* Pierre ex Pitard | Rubiaceae | 42.1 (FCC1-HN) | 157 |
| Naucleofficine C | *Nauclea officinalis* Pierre ex Pitard | Rubiaceae | 40.5 (FCC1-HN) | 157 |
| Naucleofficine D | *Nauclea officinalis* Pierre ex Pitard | Rubiaceae | 39.8 (FCC1-HN) | 157 |
| Naucleofficine E | *Nauclea officinalis* Pierre ex Pitard | Rubiaceae | 38.3 (FCC1-HN) | 157 |
| Uncarine D | *Mitragyna inermis* (Willd.) Kuntze | Rubiaceae | 46.2 (W2) | 168 |
| Maculosidine | *Vepris uguenensis* Engl. | Rutaceae | >50 (3D7/FCM29) | 65 |
| Flindersiamine | *Esenbeckia febrifuga* A.Juss. | Rutaceae | >50 (3D7/W2) | 169 |
| r-Fagarine | *Esenbeckia febrifuga* A.Juss. | Rutaceae | >50 (3D7/W2) | 169 |
| Rutaevine | *Esenbeckia febrifuga* A.Juss. | Rutaceae | >50 (3D7/W2) | 169 |
| Tegerrardin A | *Teclea gerrardii* Verdoorn | Rutaceae | 12.3 (D10) | 170 |
| Dihydroavicine | *Zanthoxylum rhoifolium* Lam. | Rutaceae | 33.0 (FcB1) | 145 |
| Fagaridine | *Zanthoxylum rhoifolium* Lam. | Rutaceae | 38.0 (FcB1) | 145 |
| 7,9-Dimethoxy-2,3-methylenedioxybenzophenanthridine | *Zanthoxylum rubescens* Planch. ex Hook. | Rutaceae | >50 (3D7/FCM29) | 171 |
| Bis[6-(5,6-dihydrochelerythrinyl)] ether | *Zanthoxylum rubescens* Planch. ex Hook. | Rutaceae | 15.3 (3D7)<br>14.9 (FCM29) | 171 |
| Zanthomamide | *Zanthoxylum rubescens* Planch. ex Hook. | Rutaceae | >50 (3D7/FCM29) | 171 |
| Lemairamide | *Zanthoxylum rubescens* Planch. ex Hook. | Rutaceae | >50 (3D7/FCM29) | 171 |
| Harmine | *Peganum harmala* L. | Zygophyllaceae | 37.7 | 172 |
| Harmaline | *Peganum harmala* L. | Zygophyllaceae | >50 | 172 |

Figure 17 shows other *N*-containing compounds with moderate or promising activity *in vitro* against various strains of *P. falciparum.*

Table 4 gives the tested alkaloids presenting low or no activity *in vitro* against various strains of *P. falciparum.*[49,65,112,144,145,147–150,157,164–172]

## Other metabolites

Two compounds were isolated from the stems and leaves of *Croton lobatus* L. (Euphorbiaceae), a medicinal plant used in western Africa in traditional folk medicine to cure malaria, pregnancy troubles and dysentery. (*Z*,*Z*,*Z*)-9,12,15-Octadecatrienoic acid methyl ester (**293**) and 8,11,17,21-tetramethyl-(*E*,*E*,*E*,*E*)-8,10,17,21-tetraentetracosanoic acid (**294**) showed some antiplasmodial activity on K1 strain, with IC50 values of 10.9 and 9.1 $\mu$M, respectively, and SI values of 18.4 and over 20, respectively.[57] Bioassay-directed fractionation of the $CHCl_3$ extract of the dried stems of *Rourea minor* (Gaertn.) Aubl. (Connoraceae) liana led to the isolation of rouremin (**295**), as well as a known compound, 1-(26-hydroxyhexacosanoyl)-glycerol (**296**). They showed activity with IC50 values of 5.1 and 9.5 $\mu$M against D6 and 4.5 and 12.7 $\mu$M against W2 strains.[45] Crypthophilic acid C (**297**) isolated from the resin of *Scrophularia cryptophilla* Boiss. & Heldr. (Scrophulariaceae) showed antimalarial activity with an IC50 of 4.1 $\mu$M.[140] Three new ether diglycosides (**298–300**), namely matayosides A–B and D, were isolated from the root bark of *Matayba guianensis* Aubl. (Sapindaceae), a plant exhibiting antiplasmodial activity. These compounds were evaluated for their antiplasmodial activity against FcB1 with IC50 values of 8.1, 4.7 and 3.5 $\mu$M.[173] Guieranone A (**301**), a naphthyl butenone, was purified from the leaves and roots of *Guiera senegalensis* J. F. Gmel. (Combretaceae). Guieranone A showed notable antiplasmodial activity (IC50 = 4.1 $\mu$M) associated with high cytotoxicity towards human monocytes.[174] From the petroleum ether extract of the root bark of *Cussonia zimmermannii* Harms (Arialaceae), two polyacetylenes were isolated, 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl ethanoate (**302**) and 16-acetoxy-11-hydroxyoctadeca-17-ene-12,14-diynyleth-

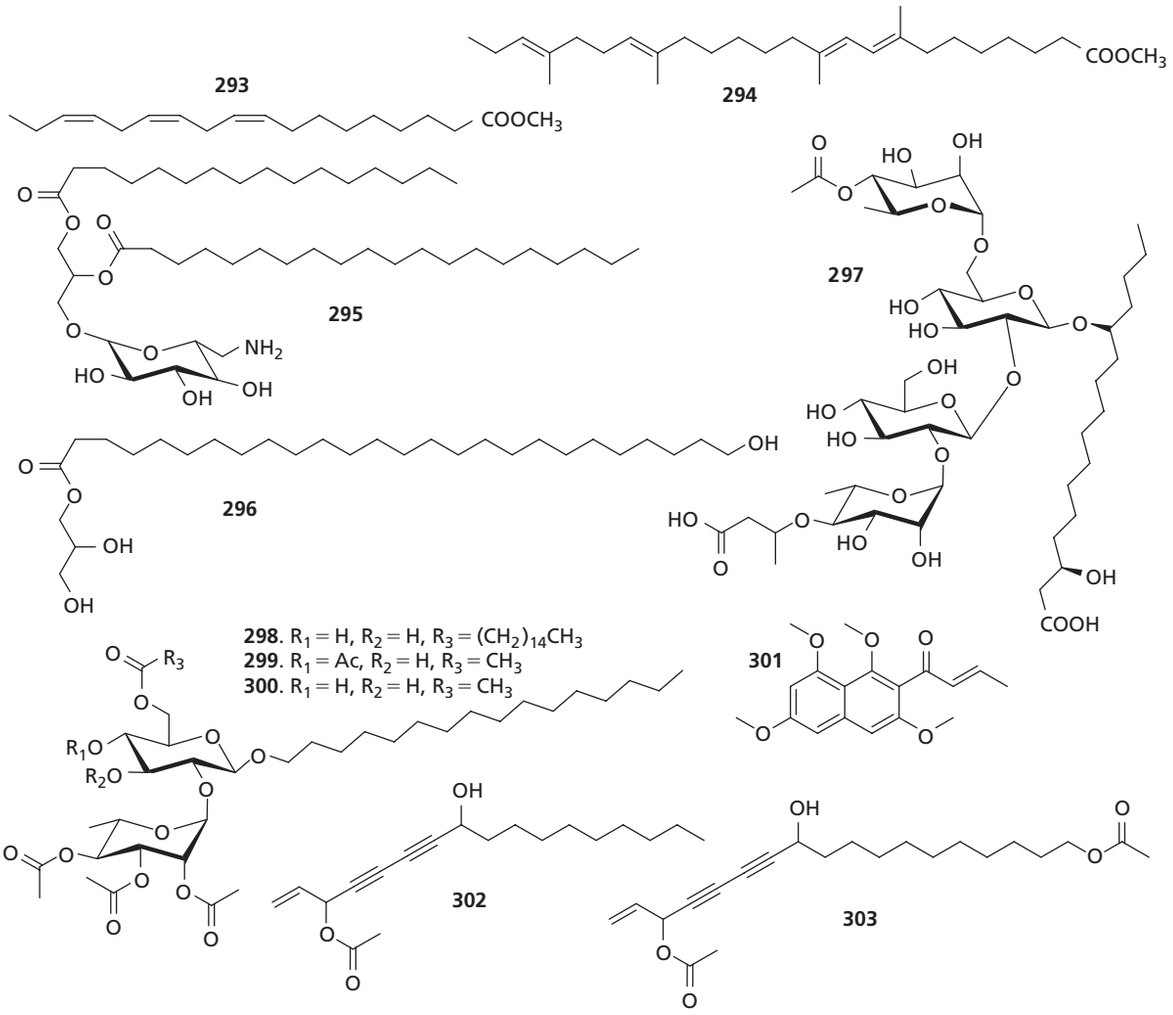



**Figure 18** Other metabolites with moderate or promising activity *in vitro* against various strains of *P. falciparum*

**Table 5** Other metabolites presenting low or no activity *in vitro* against various strains of *P. falciparum*

| Compound | Plant | Family | IC50 ($\mu$M) | Reference no. |
|---|---|---|---|---|
| 19-(2-Furyl)nonadeca-5,7-diynoic acid | *Polyalthia evecta* Finet & Gagnep. | Annonaceae | >50 (K1) | 176 |
| 8-Hydroxyheptadeca-4,6-diyn-3-yl ethanoate | *Cussonia zimmermannii* Harms | Arialaceae | 19 | 175 |
| Scleropyric acid | *Scleropyrum wallichianum* Arn. | Santalaceae | 27.3 (K1) | 177 |
| Matayoside C | *Matayba guianensis* Aubl. | Sapindaceae | 11.7 (FcB1) | 173 |

anoate (**303**). They were active with IC50 values of 1.4 and 2.2 $\mu$M, respectively.[175]

Figure 18 shows other metabolites with moderate or promising activity *in vitro* against various strains of *P. falciparum*.

Table 5 gives the tested other metabolites presenting low or no activity *in vitro* against various strains of *P. falciparum*.[173,175–177]

## Discussion

Several plants are used in traditional medicine in many countries for the treatment of malaria or symptoms of the disease. This review focused on publications from 2005 to the end of 2008, and shows that the ethnopharmacological and bio-guided fractionation approaches have led to the isolation of some promising new antimalarial compounds with a large variety of structures. About 480 compounds were isolated and evaluated for antimalarial activity *in vitro*. These compounds possess low ($11 < IC50 \leq 50$ $\mu$M), moderate ($2 < IC50 \leq 11$ $\mu$M) or promising ($IC50 \leq 2$ $\mu$M) activity *in vitro* against various strains of *P. falciparum*, which is responsible for the most severe cases of malaria. Some of the active compounds were also tested for their cytotoxicity but only a few of them were tested for their antimalarial activity *in vivo*. Nevertheless, in these cases, the

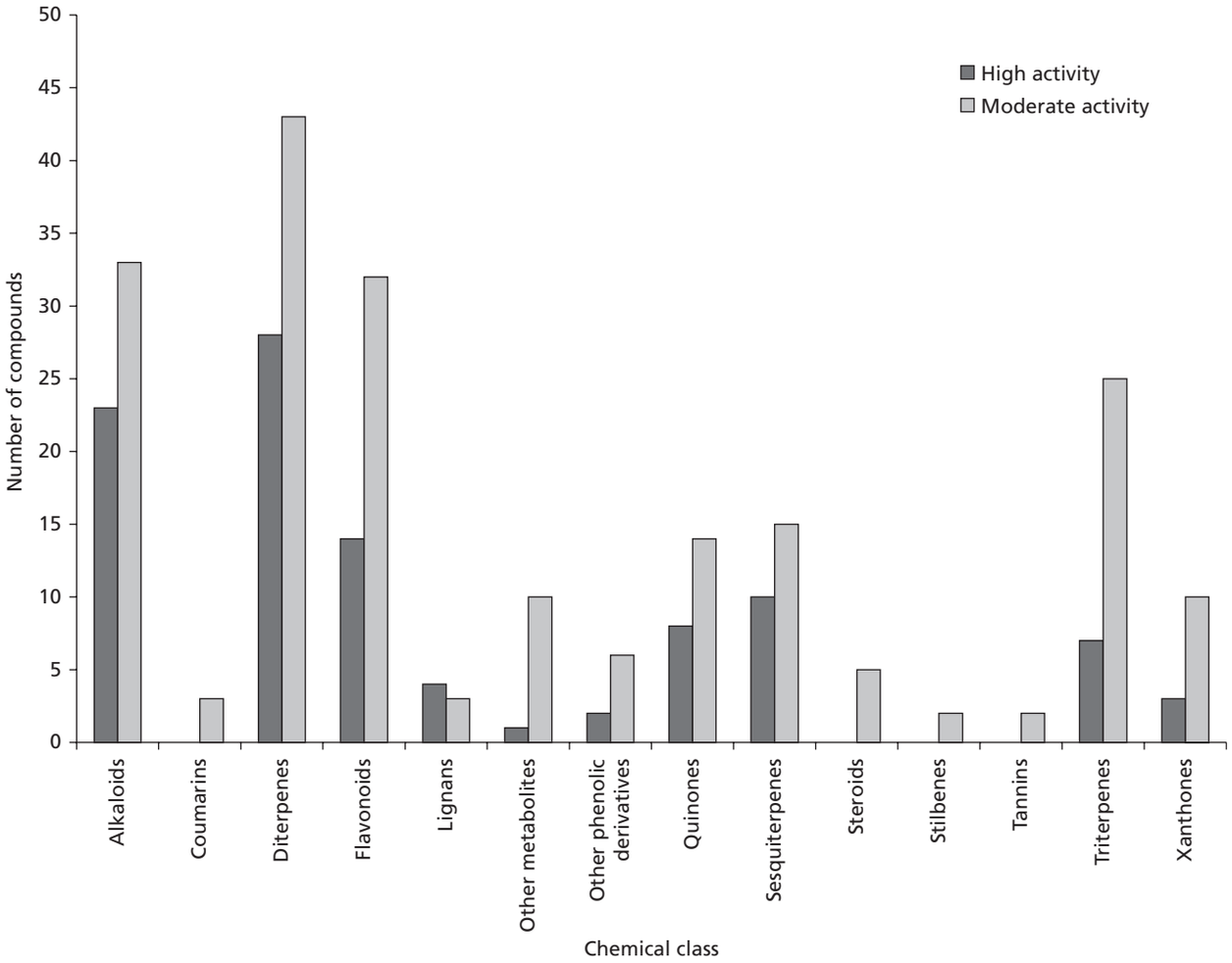



**Figure 19** Number of compounds with high ($IC50 \leq 2$ $\mu$M) or moderate ($2 < IC50 \leq 11$ $\mu$M) activity *in vitro* against various strains of *P. falciparum*, classified according to their chemical classes

promising in-vitro activity of several compounds from different chemical classes could be confirmed by in-vivo tests. Among them are several phenolic compounds: a chalcone, two stilbenes and a coumarine; terpenoids: a sesqui- and two tri-terpenes; and alkaloids: four ornithine/lysine and one tryptophane derivative. Moreover, several compounds already isolated and tested *in vitro* before 2005 were evaluated for in-vivo antimalarial activity, for example, simalikalactone D with an ED50 of 3.7 mg/kg per day orally.[178]

In traditional medicine, it is often the aqueous decoction of the plant that is used as a treatment to fight malaria. In the present study, we observed that most of the promising compounds are aglycones or other lipophilic compounds. Nevertheless, it is known that other compounds present in crude extracts, for example flavonoid heterosides or saponosides, could promote the solubilisation of more lipophilic compounds in water, supporting the implication of lipophilic compounds in the activity of water extracts.[179] We also observed that several extracts that are used in traditional medicine do not possess interesting activity *in vitro*. This may be explained by the fact that some compounds can only become active after metabolisation so they do not display good activity *in vitro*. This absence of activity could also be explained by an action on another stage of the *Plasmodium* (sporozoites, gametocytes), the in-vitro test focusing on the erythrocytic stage of the parasite (trophozoites, schizonts and merozoites). Moreover, the plants can also be used because they are effective on other symptoms of the illness such as fever, vomiting, abdominal pains and cephalgias. It can also be noted that compounds that have weak activity could promote their potential with other metabolites through a synergy of action as is often the case with crude extracts possessing several active molecules or adjuvants.

Among the compounds we reviewed, only a few of them exhibited high activity and should be considered as lead compounds for further investigation (Figures 19 and 20). When considering chemical classes and families from which active compounds (IC50 $\leq$ 2 $\mu$M) were isolated, we observed that they belong mainly to the diterpenes and alkaloids (between 20 and 30 compounds), flavonoids and sesquiterpenes (between 10 and 15 compounds), and they were isolated from several plant families. Nevertheless, some chemotaxonomical correlations could be observed.

Figures 19 and 20 show the number of compounds with high (IC50 $\leq$ 2 $\mu$M) or moderate (2 < IC50 $\leq$ 11 $\mu$M) activity

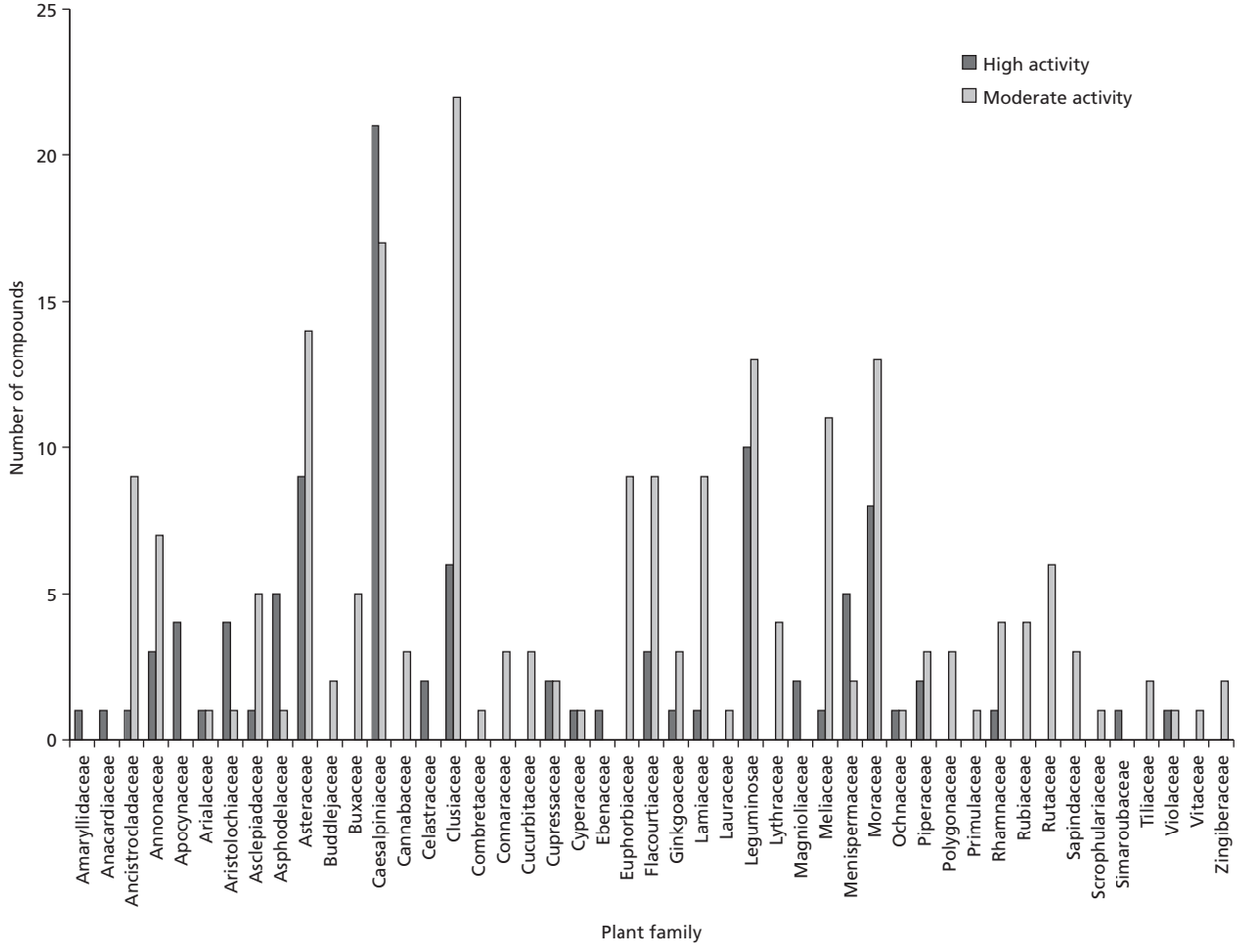



**Figure 20** Number of compounds with high (IC50 $\leq$ 2 $\mu$M) or moderate (2 < IC50 $\leq$ 11 $\mu$M) activity *in vitro* against various strains of *P. falciparum*, classified according to the plant family from which they were isolated

*in vitro* against various strains of *P. falciparum* classified according to their chemical classes and according to the plant family from which they were isolated, respectively.

The majority of active diterpenes were isolated from the Caesalpinaceae family and particularly from *Caesalipina crista* L. This plant should be further investigated and its several active cassane- and norcassane-compounds tested clinically.

There are different sources of alkaloids that have strong activity, Leguminosae, Apocynaceae, Menispermaceae and Annonaceae. Leguminosae is one of the greatest families with active alkaloids and flavonoids. The main active alkaloids were derivatives from phenylalanine and tyrosine.

Sesquiterpene lactones, like the famous artemisinin from *Artemisia annua*, have been isolated from a few plants of the Asteraceae family but most of them are also highly cytotoxic. Clusiaceae is an interesting plant family which has allowed the isolation of active quinones and xanthones. A review that covers antimalarial plant metabolites from 1990 to 2000 highlighted the importance of this family with five new active xanthones.[3]

Moraceae is a family with several interesting compounds and particularly flavonoids from *A. champeden* Spreng. In earlier years, active stilbenes were isolated from *Artocarpus integer*.[3] When examining the structures of the most active flavonoids from the last four years, we observed that most of them are prenylated compounds, thus being generally more lipophilic than non-prenylated ones. This higher lipophilicity probably increases the resorption through cell membrane, which may explain the higher activity often observed. Moreover, common dietary flavonoids possess antimalarial activity with IC50 values of between 11 and 66 $\mu$M.[180]

From the 1990s, the major compounds that showed promising activity were alkaloids from Apocynaceae and Loganiaceae, flavonoids from Fabaceae, quinones from Asphodelaceae, tannins and triterpenes from Combretaceae and butenolides from Monimiaceae.[2] In 2003, a review showed that three classes of secondary plant metabolites were mostly responsible for antimalarial activity: alkaloids, quassinoids and sesquiterpenes lactones.[5] Indeed, non-nitrogenous natural products were also shown to be promising.[7] In the present study, very active alkaloids and quinones were also isolated from Apocynaceae and Asphodelaceae families, respectively, showing the potential of these families, but other families must not be underestimated and are also worthy of evaluation.

In traditional medicine, essential oils containing mono- and sesquiterpenes are also used as antimalarials. Several studies showed the antimalarial activity of these oils from different plant species. For example, the essential oil of *Salvia repens* exhibited an IC50 of 1.7 $\mu$g/ml with $\beta$-phellandrene, $\beta$-caryophyllene, limonene and camphor as major components.[181] Nevertheless, the effect of isolated compounds was not evaluated and so they are not listed here.

## Conclusions

A large number of antimalarial compounds with a wide variety of structures have been isolated from plants and can play a role in the development of new antimalarial drugs. Ethnopharmacological approach appears to be a promising way to find plant metabolites that could be used as templates for designing new derivatives with improved properties.

## Declarations

### Conflict of interest

Michel Frédérich is a senior research associate from the FNRS.

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