12193014
Abegaz BM, Bezabih M, Msuta T, Brun R, Menche D, Muhlbacher J, Bringmann G
Gaboroquinones A and B and 4'-O-demethylknipholone-4'-O-beta-D-glucopyranoside, phenylanthraquinones from the roots of Bulbine frutescens.
J Nat Prod. 2002 Aug;65(8):1117-21.
The novel phenylanthraquinones 4'-O-demethylknipholone-4'-O-beta-D-glucopyranoside (2) and gaboroquinones A (3) and B (4) were isolated from the African medicinal plant Bulbine frutescens. Biaryl 2 represents the first phenylanthraquinone glucoside, while 3 and 4 are the first side-chain-hydroxylated phenylanthraquinones. Their constitutions were determined by spectroscopic analysis, in particular by HMBC, HMQC, and ROESY NMR investigations, and by chemical transformations. The axial configurations were elucidated chemically, by deglucosylation of 2 and by side-chain deoxygenation of 3 and 4 to give the known phenylanthraquinones 4'-O-demethylknipholone (5), isoknipholone (6), and knipholone (1), respectively, and chiroptically, by CD investigations. Compounds 2, 3, and 4 showed moderate to good antiplasmodial and antitrypanosomal activities in vitro.

15032466
Abo KA, Kinghorn AD
Isolation of an anti-tumour terpenoid from stem bark of Spondianthus preussii var. preussii Engl.
Afr J Med Med Sci. 2003 Jun;32(2):179-82.
We report a biologically monitored phytochemical separation of stem bark of Spondianthus preussii var. preussii against a panel of human cancer cell lines in vitro and the P-388 murine lymphocytic leukemia cells in culture. An ethylacetate extract of the stem bark exhibited selective cytotoxicity against human melanoma (ED50 = 10.0 ug/ml). Further activity-guided fractionation of the ethylacetate extract by flash chromatography and subsequent purification on preparative thin layer chromatography led to the identification of a lupane-type triterpene, 3beta-hydroxy-20(29)--lupenoic acid, by spectroscopic methods. This is the first report of the occurrence of this compound in S. preussii var. preussii. It is also the first time this triterpene is being shown to exhibit in vitro anti-tumor activity against human melanoma (ED50 = 2.4 ug/ml). This compound could be a promising bioactive natural product since it has been previously reported to exhibit a range of biological activities including in vivo and in vitro antiplasmodial activity and it is not toxic.

11547422
Abreu P, Pereira A
New indole alkaloids from Sarcocephalus latifolius.
Nat Prod Lett. 2001;15(1):43-8.
Phytochemical investigation of the root extract of Sarcocephalus latifolius has led to the isolation of the new indole alkaloids 21-O-methylstrictosamide aglycone and 21-O-ethylstrictosamide aglycone, together with strictosamide, angustine, nauclefine, angustidine, angustoline, 19-O-ethylangustoline, naucleidinal, 19-epi-naucleidinal, quinovic acid-3 beta-O-beta-D-fucopyranoside, quinovic acid-3 beta-O-alpha-L-rhamnopyranoside, scopoletin, and beta-sitosterol. Strictosamide displayed moderate antiplasmodial activity against Plasmodium falciparum.

11378289
Addae-Kyereme J, Croft SL, Kendrick H, Wright CW
Antiplasmodial activities of some Ghanaian plants traditionally used for fever/malaria treatment and of some alkaloids isolated from Pleiocarpa mutica; in vivo antimalarial activity of pleiocarpine.
J Ethnopharmacol. 2001 Jun;76(1):99-103.
Fourteen Ghanaian plants used in folk medicine to treat fever/malaria were screened for activity against Plasmodium falciparum (strain K1) and were tested for general toxicity to the brine shrimp. Extracts from three of the plants, Pleiocarpa mutica, Cleistopholis patens and Uvaria chamae were found to have significant antiplasmodial activity. The extract of U. chamae was toxic to brine shrimps. These findings lend support to the use of these plants in traditional medicine. Possible toxicity due to U. chamae is a cause for concern. Five known alkaloids, pleiocarpine (1), kopsinine (2), pleiocarpamine (3), eburnamine (4) and pleiomutinine (5) were isolated from the roots of P. mutica. This is the first report of the occurrence of (4) in P. mutica. Compound (5) was the most active against P. falciparum (IC50 = 5 microM). Although (1) was inactive against malaria parasites in vitro, it was moderately active against P. berghei in mice (25 mg kg(-1) daily for 4 days reduced parasitaemia by 28.5% compared to untreated controls).

12963153
Adzu B, Abbah J, Vongtau H, Gamaniel K
Studies on the use of Cassia singueana in malaria ethnopharmacy.
J Ethnopharmacol. 2003 Oct;88(2-3):261-7.
Cassia singueana (Family: Fabaceae) is used in northern Nigeria for the treatment of acute malaria attack. We investigated the activities of the methanol extract of the root bark of this plant against rodent plasmodia

infection, nociception, pyrexia and inflammation in mice and rats. The studies were carried out using acetic acid-induced writhing, hot plate algesia, rodent plasmodia (Plasmodium berghei) in mice; formalin test, yeast-induced pyrexia and egg-albumin-induced inflammation in rats. The results showed that the extract exhibited significant antinociceptive, antipyretic and antiplasmodial activity in all the models used. Phytochemical screening of the extract revealed the presence of phenols, saponins, tannins and some traces of anthraquinones. The LD50 of the extract was established to be 847+/-30 mg/kg, i.p. in mice. The observed pharmacological activities might be the scientific basis for the folkloric use of the plant in treating acute malaria attack. The study also paves way for the possible development of it, as a phytodrug against malaria.

12444453
Akaki M, Nakano Y, Ito Y, Nagayasu E, Aikawa M
Effects of dipyridamole on Plasmodium falciparum-infected erythrocytes.
Parasitol Res. 2002 Dec;88(12):1044-50. Epub 2002 Aug 1.
This study assessed the antimalarial activity of dipyridamole, a well-known vasodilator and inhibitor of platelet aggregation. Dipyridamole was effective against all of the erythrocytic stages such as rings, trophozoites and schizonts, and induced ultrastructural changes during the transition from trophozoite to schizont in vitro. Merozoites were also inhibited from invading dipyridamole-treated erythrocytes. It seems that dipyridamole binds to the erythrocyte membrane blocking the receptors for the merozoite. The 50% inhibitory concentration (IC(50)) of dipyridamole against Plasmodium falciparum infection was 30 nM. The IC(50) of chloroquine decreased from 97.0 nM to 13.7 nM when combined with dipyridamole (0.1 nM). Therefore, we suggest that dipyridamole has antiplasmodial activity due to its ability to arrest parasite development and by inhibiting merozoite invasion of the erythrocytes. Chloroquine activity against P. falciparum is also enhanced by the addition of dipyridamole. Treatment with a combination of chloroquine and dipyridamole may lead to a more effective treatment for chloroquine-resistant strains of P. falciparum.

11859471
Akendengue B, Ngou-Milama E, Roblot F, Laurens A, Hocquemiller R, Grellier P, Frappier F
Antiplasmodial activity of Uvaria klaineana.
Planta Med. 2002 Feb;68(2):167-9.
Crude extracts of Uvaria klaineana Engler and Diels (Annonaceae) stems showed in vitro activity against chloroquine-resistant K1 strain of Plasmodium falciparum. The most active extract was the basic dichloromethane extract containing crude alkaloids (IC50 = 3.55 microg/mL). The bioassay-guided fractionation of this extract led to the isolation of the major alkaloid crotsparine (1) which showed an antiplasmodial activity against the chloroquine-sensitive Thai strain of P. falciparum and the chloroquine-resistant K1 and FcB1 strains of P. falciparum. Two minor alkaloids were also identified as crotonosine (2) and zenkerine (3). Their structures were elucidated using 2D-NMR techniques.

12426089
Ali H, Konig GM, Khalid SA, Wright AD, Kaminsky R
Evaluation of selected Sudanese medicinal plants for their in vitro activity against hemoflagellates, selected bacteria, HIV-1-RT and tyrosine kinase inhibitory, and for cytotoxicity.
J Ethnopharmacol. 2002 Dec;83(3):219-28.
Ethnobotanical investigations led to the selection of 19 plant species, used traditionally in Sudan against malaria and other similar tropical diseases, for further studies. Pamianthe peruviana (Amaryllidaceae) exhibited significant activity against a chloroquine-resistant Plasmodium falciparum strain (K1) and a chloroquine-sensitive strain (NF54) with IC(50) values of 0.6 and 1.1 microg/ml, respectively. Additionally, P. peruviana showed considerable activities against Trypanosoma brucei rhodesiense (IC(50) 1.5 microg/ml) and T. cruzi (IC(50) 11.8 microg/ml). The antiplasmodial activity of the different extracts of Salvadora persica (Salvadoraceae) against P. falciparum NF54 strain were found to be 0.6 microg/ml (stems) and 0.7 microg/ml (leaves). Extracts of different parts of Combretum hartmannianum (Combretaceae) possessed significant activity against the chloroquine-sensitive P. falciparum strain (NF54) with IC(50) values of 0.2 microg/ml (bark), 0.4 microg/ml (stem) and 4.3 microg/ml (leaves). Most interestingly, the extracts of the leaves of C. hartmannianum totally inhibited the enzyme HIV-1 reverse transcriptase (HIV-1 RT) at a concentration of 66 microg/ml. A comparably strong activity against p56(lck) tyrosine kinase was also seen for this extract.

16491458
Andayi AW, Yenesew A, Derese S, Midiwo JO, Gitu PM, Jondiko OJ, Akala H, Liyala P, Wangui J, Waters NC, Heydenreich M, Peter MG
Antiplasmodial flavonoids from Erythrina sacleuxii.
Planta Med. 2006 Feb;72(2):187-9.

The acetone extracts of the root bark and stem bark of Erythrina sacleuxii showed antiplasmodial activities against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of Plasmodium falciparum. Chromatographic separation of the acetone extract of the root bark afforded a new isoflavone, 7-hydroxy-4'-methoxy-3'-prenylisoflavone (trivial name 5-deoxy-3'-prenylbiochanin A) along with known isoflavonoids as the antiplasmodial principles. Flavonoids and isoflavonoids isolated from the stem bark of E. sacleuxii were also tested and showed antiplasmodial activities. The structures were determined on the basis of spectroscopic evidence.

16095316
Andre-Barres C, Najjar F, Bottalla AL, Massou S, Zedde C, Baltas M, Gorrichon L
Fe(II)-induced reduction of labelled endoperoxides. NMR degradation studies on G3 factor and its methyl ether.
J Org Chem. 2005 Aug 19;70(17):6921-4.
The behavior of G3 factor and of its methylated or fluorinated analogues G3Me and G3F, was studied under Fe(II) conditions. Degradation products were isolated and characterized in each case. The use of labelled compounds allowed us to propose mechanisms in which a tertiary radical is involved. This radical rearranges by 5-exo-trig cyclization, or disproportionates in the case of G3Me. A correlation between antiplasmodial activity and stability of this radical is proposed.

11746852
Antoun MD, Ramos Z, Vazques J, Oquendo I, Proctor GR, Gerena L, Franzblau SG
Evaluation of the flora of Puerto Rico for in vitro antiplasmodial and antimycobacterial activities.
Phytother Res. 2001 Nov;15(7):638-42.
The emergence of resistant strains of Plasmodium falciparum and Mycobacterium tuberculosis underscores the need for novel drugs that are effective against these microorganisms. As part of our screening programme of the flora of Puerto Rico, we tested a number of ethanol extracts of higher plants for antiplasmodial and antimycobacterial activities. A total of 40 extracts belonging to 23 plant families and 37 species were tested for antiplasmodial activity. Five extracts demonstrated activity against Plasmodium falciparum in vitro (50%-100% parasite suppression at 5 microg/mL). Another 63 extracts belonging to 30 plant families and 50 species were tested in vitro against Mycobacterium tuberculosis. Two extracts were found to be active, Ficus citrifolia and Pisonia borinquena (85% or more inhibition of microbial growth at 100 microg/mL of extract).

11300877
Arzel E, Rocca P, Grellier P, Labaeid M, Frappier F, Gueritte F, Gaspard C, Marsais F, Godard A, Queguiner G
New synthesis of benzo-delta-carbolines, cryptolepines, and their salts: in vitro cytotoxic, antiplasmodial, and antitrypanosomal activities of delta-carbolines, benzo-delta-carbolines, and cryptolepines.
J Med Chem. 2001 Mar 15;44(6):949-60.
The paper describes, in its first part, a new synthesis of benzo-delta-carbolines, cryptolepines, and their salts. The strategy is based on the association between halogen-dance and hetero-ring cross-coupling. It is fully convergent and regioselective with interesting overall yields from 27% to 70%. A halogen-dance mechanism in quinoline series is also proposed. The formal synthesis of potential antimalarial compounds and the first total synthesis of 11-isopropylcryptolepine are also described. In the second part, cytotoxic activity against mammalian cells and activities against Plasmodium falciparum and Trypanosoma cruzi of benzo-delta-carbolines and delta-carbolines were evaluated in vitro to study the structure-activity relationships. For benzo-delta-carbolines, methylation at N-5 increases the cytotoxic and antiparasitic activities. A further alkylation on C-11 generally increases the cytotoxic activity but not the antiparasitic activity, cryptolepine and 11-methylcryptolepine being the most active on both parasites. Taking advantage of the fluorescence of the indoloquinoline chromophore, cryptolepine was localized by fluorescence microscopy in parasite DNA-containing structures suggesting that these compounds act through interaction with parasite DNA as proposed for cryptolepine on melanoma cells. For delta-carbolines, methylation at N-1 is essential for the antimalarial activity. 1-Methyl-delta-carboline specifically accumulates in the intracellular parasite. It has weak cytotoxic activity and can be considered as a potential antimalarial compound.

15104493
Asili J, Lambert M, Ziegler HL, Staerk D, Sairafianpour M, Witt M, Asghari G, Ibrahimi IS, Jaroszewski JW
Labdanes and isopimaranes from Platycladus orientalis and their effects on erythrocyte membrane and on Plasmodium falciparum growth in the erythrocyte host cells.
J Nat Prod. 2004 Apr;67(4):631-7.
Six labdanes (1-6) and four isopimaranes (7-10), including three new natural products (7, 9, and 10), were isolated from Platycladus orientalis, and their structures determined using 1D and 2D NMR methods, ion-

cyclotron resonance HRMS, and optical rotation data. Relative configurations of all chiral centers in the isopimaranes were determined using NOESY experiments at 600 and 800 MHz. Specific optical rotation data were used to correlate absolute configurations. Compounds 1-9 and aframodial (11) were tested for their in vitro antiplasmodial activity and for their ability to induce changes of erythrocyte shape in order to obtain data about possible correlation between the two effects. All compounds tested exhibited weak (IC(50) > 25 microM) in vitro antiplasmodial effects against Plasmodium falciparum strain 3D7. At the same time, the compounds caused echinocytic or stomatocytic changes of the erythrocyte membrane curvature, indicative of their incorporation into the lipid bilayer, in the concentration region where the antiplasmodial activity was observed. The antiplasmodial effect of these compounds thus appears to be an indirect effect on the erythrocyte host cell. Weak or moderate antiplasmodial activity observed with many other apolar natural products, in particular those with amphiphilic structures, is also likely to be an indirect effect.

11746844
Asres K, Bucar F, Knauder E, Yardley V, Kendrick H, Croft SL
In vitro antiprotozoal activity of extract and compounds from the stem bark of Combretum molle.
Phytother Res. 2001 Nov;15(7):613-7.
The antiprotozoal activity of the Ethiopian medicinal plant Combretum molle (R. Br. ex G. Don.) Engl & Diels (Combretaceae) was evaluated by in vitro testing against Plasmodium falciparum, Trypanosoma brucei rhodesiense, Trypanosoma cruzi and Leishmania donovani. The acetone fraction of the stem bark of this plant prepared by soxhlet extraction was inactive against the intracellular amastigotes of L. donovani and T. cruzi in murine peritoneal macrophages but showed significant activity against extracellular T. b. rhodesiense blood stream form trypomastigotes and trophozoites of P. falciparum with IC(50) values of 2.19 and 8.17 microg/mL, respectively. Phytochemical examination of the bioactive fraction resulted in the isolation of two tannins and two oleanane-type pentacyclic triterpene glycosides. One of the tannins was identified as the ellagitannin, punicalagin, whilst the structure of the other (CM-A) has not yet been fully elucidated. The saponins that were characterized as arjunglucoside (also called 4-epi-sericoside) and sericoside displayed no activity against any of the four species of protozoa tested. On the other hand, punicalagin and CM-A had IC(50) values of 1.75 and 1.50 microM, respectively, against T. b. rhodesiense and were relatively less toxic to KB cells (cytotoxic/antiprotozoal ratios of 70 and 48, respectively). The tannins also showed intermediate activity against P. falciparum, although their selectivity against these parasites was less favourable than the above. It appears that our findings are the first report of hydrolysable tannins exhibiting antitrypanosomal and antiplasmodial activities.

16394561
Azebaze AG, Meyer M, Valentin A, Nguemfo EL, Fomum ZT, Nkengfack AE
Prenylated xanthone derivatives with antiplasmodial activity from Allanblackia monticola STANER L.C.
Chem Pharm Bull (Tokyo). 2006 Jan;54(1):111-3.
Further study of the methanol extract of the stem bark of Allanblackia monticola STANER L.C. resulted in the isolation of a new prenylated xanthenedione, designated allanxanthone C, together with the five known xanthones, garciniafuran, tovophyllin A, rubraxanthone, norcowanin and mangostin and one saponin, stigmasterol-3-O-beta-D-glucopyranoside. The structure of the new compound was established by detailed spectroscopic analysis to be 1,2-dihydro-3,6,8-trihydroxy-1,1,7-tri(3-methylbut-2-enyl)xanthen-2,9-dion e (3-hydroxyapetalinone C). The methanol extract and pure compounds were tested on two strains of Plasmodium falciparum, F32 (chloroquine sensitive) and FcM29 (chloroquine resistant). The IC50 values obtained ranged from 0.6 to 8.9 microg/ml. Their cytotoxicity was estimated on human melanoma cells (A375) and the cytotoxicity/antiplasmodial ratio was found to be between 15.45 and 30.46. The antimicrobial activities against a range of microorganisms of the crude extract and some of these compounds are also reported.

12350157
Ballin NZ, Traore M, Tinto H, Sittie A, Molgaard P, Olsen CE, Kharazmi A, Christensen SB
Antiplasmodial compounds from Cochlospermum tinctorium.
J Nat Prod. 2002 Sep;65(9):1325-7.
Fractionation of an ethanol extract of roots of Cochlospermum tinctorium afforded five compounds: 3-O-E-p-coumaroylalphitolic acid (1), cochloxanthin (2), dihydrocochloxanthin (3), alphitolic acid (4), and 1-hydroxytetradecan-3-one (5). This is the first example of a 1-hydroxyalkan-3-one obtained from plant material after gentle workup. The antiplasmodial activities of the compounds were determined, and the IC(50) value of 3-O-E-p-coumaroylalphitolic acid was 2.3 microM.

12127243
Banzouzi JT, Prado R, Menan H, Valentin A, Roumestan C, Mallie M, Pelissier Y, Blache Y
In vitro antiplasmodial activity of extracts of Alchornea cordifolia and identification of an active constituent: ellagic acid.

J Ethnopharmacol. 2002 Aug;81(3):399-401.
Extracts of leaves of Alchornea cordifolia were studied for their antiplasmodial activities. Chloroformic and ether extracts were found to be inactive while the ethanolic extract exhibited mild in vitro activity against Plasmodium falciparum. Fractionation of this extract led us to isolate ellagic acid as the active constituent of the extract with IC(50) in the range of 0.2-0.5 microM. Cytotoxicity of ethanolic fraction and ellagic acid was also estimated on human fibroblasts cells (IC(50) on Hela cells = 7.3 microM at 24 h for ellagic acid).

15185848
Banzouzi JT, Prado R, Menan H, Valentin A, Roumestan C, Mallie M, Pelissier Y, Blache Y
Studies on medicinal plants of Ivory Coast: investigation of Sida acuta for in vitro antiplasmodial activities and identification of an active constituent.
Phytomedicine. 2004;11(4):338-41.
Sida acuta Burm. (Malvaceae) originating from Ivory Coast was selected after an ethnobotanical survey: traditional healers of malaria commonly used this plant for the treatment. Extracts were tested on two strains of Plasmodium falciparum: FcM29-Cameroon (chloroquine-resistant strain) and a Nigerian chloroquine-sensitive strain. Extracts were obtained by preparing decoction in water of the powdered plant, the technique used by most of the traditional healers. An ethanol extract was then made and tested. The IC50 values obtained for these extracts ranged from 3.9 to -5.4 microg/ml. Purification of this active fraction led to the identification of cryptolepine as the active antiplasmodial constituent of the plant.

15103672
Beha E, Jung A, Wiesner J, Rimpler H, Lanzer M, Heinrich M
Antimalarial activity of extracts of Abutilon grandiflorum G. Don - a traditional Tanzanian medicinal plant.
Phytother Res. 2004 Mar;18(3):236-40.
The Tanzanian medicinal plant Abutilon grandiflorum G. Don was studied for its in vivo and in vitro antiplasmodial effects. The ethyl acetate extract showed prominent in vivo activity against P. vinckei vinckei in mice and in vitro against P. falciparum strains HB3 and FCB. The extract was only moderately cytotoxic if tested in vitro against the colon cell line HT29. In the in vivo study, the results were significantly influenced by the treatment schedule used, i.e. early treatment with higher doses was more successful than applying the same overall amount over a longer period. Phytochemical analysis of the extract provided no conclusive evidence for the observed parasitological effects.

14640516
Beldjoudi N, Mambu L, Labaied M, Grellier P, Ramanitrahasimbola D, Rasoanaivo P, Martin MT, Frappier F.
Flavonoids from Dalbergia louvelii and their antiplasmodial activity.
J Nat Prod 2003
Four new flavonoids (1-4), along with 13 known compounds, were isolated from the heartwood of Dalbergia louvelii by following their potential to inhibit in vitro the growth of Plasmodium falciparum. Of the isolated compounds, four known compounds showed antiplasmodial activity with IC(50) values ranging from 5.8 to 8.7 microM, namely, (R)-4' '-methoxydalbergione (5), obtusafuran (6), 7,4'-dihydroxy-3'-methoxyisoflavone (7), and isoliquiritigenin (8). The structures of the new compounds were determined using spectroscopic techniques as 1-(3-hydroxyphenyl)-3-(4-hydroxy-2,5-dimethoxyphenyl)propane (1), spirolouveline (2), (3R)-7,2'-dihydroxy-4',5'-dimethoxyisoflavanone (3), and 3-(2,4-dihydroxy-5-methoxy)phenyl-7-hydroxycoumarin (4), respectively.

12620327
Benoit-Vical F, Imbert C, Bonfils JP, Sauvaire Y
Antiplasmodial and antifungal activities of iridal, a plant triterpenoid.
Phytochemistry. 2003 Mar;62(5):747-51.
Iridal, a triterpenoidic compound extracted from Iris germanica L., was previously shown to have an interesting activity on two cultured human tumor cell lines (A2780 and K562). In the present work, this same product was tested in vitro on Plasmodium falciparum chloroquine-resistant and -sensitive strains, in vivo on P. vinckei, and on some Candida albicans and C. parapsilosis strains too. The IC(50) obtained in vitro on human malaria strain ranged from 1.8 to 26.0 microg/ml and the ED(50) in vivo is about 85 mg/kg/day by intraperitoneal route. The minimal inhibitory concentrations were higher than to 50 microg/ml, whatever the strain of yeast tested. This product presents an antiplasmodial activity similar to that obtained with extracts from the plant Azadirachta indica classically taken as reference in malaria phytomedicine. Conversely iridal shows no important antifungal activity. The specific activity of iridal on human malaria parasite and on tumor cell lines is discussed.

11458451
Bezabih M, Abegaz BM, Dufall K, Croft K, Skinner-Adams T, Davis TM

Antiplasmodial and antioxidant isofuranonaphthoquinones from the roots of Bulbine capitata.
Planta Med. 2001 Jun;67(4):340-4.
The roots of B. capitata yielded the new compounds 5,8-dihydroxy-1-tigloylmethylnaphtho[2,3-c]furan-4,9-dione, 1-acetoxymethyl-8-hydroxynaphtho[2,3-c]furan-4,9-dione, and 1-acetoxymethyl-5,8-dihydroxynaphtho[2,3-c]furan-4,9-dione, in addition to the known compounds chrysophanol, 10,10'-chrysophanol bianthrone, 8-hydroxy-1-methylnaphtho[2,3-c]furan-4,9-dione, 5,8-dihydroxy-1-methylnaphtho[2,3-c]furan-4,9-dione, 5,8-dihydroxy-1-hydroxymethylnaphtho[2,3-c]furan-4,9-dione, and 8-hydroxy-5-methoxy-1-methylnaphtho[2,3-c]furan-4,9-dione, or 5-hydroxy-8-methoxy-1-methylnaphtho[2,3-c]furan-4,9-dione. The new as well as the known isofuranonaphthoquinones showed antioxidant and weak antiplasmodial activities.

15537352
Biot C, Bauer H, Schirmer RH, Davioud-Charvet E
5-substituted tetrazoles as bioisosteres of carboxylic acids. Bioisosterism and mechanistic studies on glutathione reductase inhibitors as antimalarials.
J Med Chem. 2004 Nov 18;47(24):5972-83.
Plasmodium parasites are exposed to elevated fluxes of reactive oxygen species during intraerythrocytic life. The most important antioxidative systems are based on the glutathione reductases of the malarial parasite Plasmodium falciparum and the host erythrocyte. The development of menadione chemistry has led to the selection of the carboxylic acid 6-[2'-(3'-methyl)-1',4'-naphthoquinolyl] hexanoic acid M(5) as an inhibitor of the parasitic enzyme. As reported here, revisiting the mechanism of M(5) action revealed an uncompetitive inhibition type with respect to both NADPH and glutathione disulfide. Masking the polarity of the acidic function of M(5) by ester or amide bonds improved antiplasmodial activity. Bioisosteric replacement of the carboxylic function by tetrazole to increase bioavailability and to maintain comparable acidity led to improved antimalarial properties as well, but only with the cyanoethyl-protected tetrazoles. Using computed ab initio quantum methods, detailed analyses of the electronic profiles and the molecular properties evidenced the similarity of M(5) and the bioisoteric tetrazole T(4). The potential binding site of these molecules is discussed in light of the recently solved crystallographic structure of P. falciparum enzyme.

15934779
Biot C, Taramelli D, Forfar-Bares I, Maciejewski LA, Boyce M, Nowogrocki G, Brocard JS, Basilico N, Olliaro P, Egan TJ
Insights into the mechanism of action of ferroquine. Relationship between physicochemical properties and antiplasmodial activity.
Mol Pharm. 2005 May-Jun;2(3):185-93.
Ferroquine (FQ) is a 4-aminoquinoline antimalarial which contains a quinoline nucleus similar to chloroquine, but a novel ferrocenic group in its side chain. Previous work has demonstrated that this compound has excellent activity against malaria parasites, both in vitro and in vivo, with especially good activity against chloroquine-resistant parasites, but details of its mechanism of action have not previously been reported. In this study, we have investigated the physicochemical properties of FQ for comparison with chloroquine (CQ). Like CQ, FQ forms complexes with hematin in solution (log K = 4.95 +/- 0.05). FQ is an even stronger inhibitor of beta-hematin formation than CQ (IC(50) = 0.78 equiv relative to hematin for FQ vs 1.9 for CQ). These data suggest that the mechanism of action of FQ is likely to be similar to that of CQ and probably involves hematin as the drug target and inhibition of hemozoin formation. However, both the basicity and lipophilicity of FQ are significantly different from those of CQ. The lipophilicity of FQ and CQ are similar when protonated at the putative food vacuole pH of 5.2 (log D = -0.77 and -1.2 respectively), but differ markedly at pH 7.4 (log D = 2.95 and 0.85 respectively). In addition, the pK(a) values of FQ are lower (pK(a1) = 8.19 and pK(a2) = 6.99) than those of CQ (10.03 and 7.94, respectively). This suggests that there will be somewhat less vacuolar accumulation of FQ compared with CQ. Single crystal structure determination of FQ shows the presence of a strong internal hydrogen bond between the 4-amino group and the terminal N atom. This, together with the electron donating properties of the ferrocene moiety, probably explains the decreased pK(a). Interestingly, the decreased accumulation arising from the less basic behavior of this compound is partly compensated for by its stronger beta-hematin inhibition. Increased lipophilicity, differences in geometric and electronic structure, and changes in the N-N distances in FQ compared to CQ probably explain its activity against CQ-resistant parasites.

12116880
Blair S, Mesa J, Correa A, Carmona-Fonseca J, Granados H, Saez J
Antimalarial activity of neurolenin B and derivates of Eupatorium inulaefolium (Asteraceae).
Pharmazie. 2002 Jun;57(6):413-5.
Dried stems and leaves of Eupatorium inulaefolium (Austroeupatorium inulaefolium) (Asteraceae) were used to obtain four crude extracts (hexane, dichloromethane, methanol and ethanol). Two fractions were obtained from the hexane extract (S1 and S2) and three compounds (neurolenin B, lobatin A and lobatin B) from the

dichloromethane extract. The ethanol, hexane, dichloromethane and methanol extracts, two fractions from the hexane extract (S1 and S2), and neurolenin B were evaluated in vitro against Plasmodium falciparum, FCB-2 strain. Two extracts (dichloromethane and methanol), the S2 fraction and neurolenin B showed statistically significant antiplasmodial activity.

14510589
Bringmann G, Dreyer M, Faber JH, Dalsgaard PW, Staerk D, Jaroszewski JW, Ndangalasi H, Mbago F, Brun R, Reichert M, Maksimenka K, Christensen SB
Ancistrotanzanine A, the first 5,3'-coupled naphthylisoquinoline alkaloid, and two further, 5,8'-linked related compounds from the newly described species Ancistrocladus tanzaniensis.
J Nat Prod. 2003 Sep;66(9):1159-65.
The first phytochemical investigation of the recently discovered East African liana Ancistrocladus tanzaniensis is described, resulting in the isolation and structural elucidation of two new naphthylisoquinoline alkaloids, ancistrotanzanines A (5) and B (6), and the known compound ancistrotectoriline A (7). Ancistrotazanine A (5) represents a hitherto unprecedented 5,3'-coupling type between the naphthalene and isoquinoline portions, while 6 and 7 are 5,8'-coupled. The structures of the compounds were determined by spectroscopic, chemical, and chiroptical methods. Compounds 5 and 6 showed good activities against the pathogens of leishmaniasis and Chagas' disease, Leishmania donovani and Trypanosoma cruzi, while 5-7 displayed moderately potent antiplasmodial activities against Plasmodium falciparum parasites.

10870189
Bringmann G, Gunther C, Saeb W, Mies J, Brun R, Assi LA
8-O-methyldioncophyllinol B and revised structures of other 7,6'-coupled naphthylisoquinoline alkaloids from Triphyophyllum peltatum (Dioncophyllaceae).
Phytochemistry. 2000 Jun;54(3):337-46.
The isolation and structural elucidation of a new naphthylisoquinoline alkaloid, 8-O-methyldioncophyllinol B, from Triphyophyllum peltatum (Hutch. et Dalz.) Airy Shaw (Dioncophyllaceae) is described, together with the revised structures of other 'B-type' compounds previously misidentified as dioncophylline D, dioncophyllinol D, and 8-O-methyldioncophylline D. All of the presently described structures are 7,6'-coupled and thus have to be addressed as 'B-type' naphthylisoquinoline alkaloids. This is in contrast to the initially defined 'D-type' structures, which are 7,8'-coupled as confirmed by a total synthesis of dioncophylline D. Some of these natural and synthetic naphthylisoquinolines were found to display good in vitro antiplasmodial activities.

10630123
Bringmann G, Menche D, Bezabih M, Abegaz BM, Kaminsky R
Antiplasmodial activity of knipholone and related natural phenylanthraquinones.
Planta Med. 1999 Dec;65(8):757-8.
phenylanthraquinone knipholone (1) and three of its natural derivatives as well as seven structurally related but simplified compounds have been examined for their antiplasmodial activity against asexual erythrocytic stages of two strains of Plasmodium falciparum in vitro (K1/chloroquine-resistant and NF 54/chloroquine-sensitive). All the phenylanthraquinones showed considerable activity with only little cytotoxicity, while their anthraquinone and phenyl moieties were completely inactive. Knipholone (1) and its natural derivatives can therefore be considered as a new group of potential antimalarials

12153257
Bringmann G, Menche D, Kraus J, Muhlbacher J, Peters K, Peters EM, Brun R, Bezabih M, Abegaz BM
Atropo-enantioselective total synthesis of knipholone and related antiplasmodial phenylanthraquinones.
J Org Chem. 2002 Aug 9;67(16):5595-610.
The "lactone concept" has been efficiently employed for the first atropo-enantioselective synthesis of knipholone and related natural phenylanthraquinones. Besides the regio- and stereoselective construction of the biaryl axis, another important step was the "synthetically late" introduction of the C-acetyl group, either by a Friedel-Crafts type acetylation or by an ortho-selective Fries rearrangement first tested on simplified model systems and subsequently applied to the highly atroposelective preparation of the natural products and of simplified analogs thereof for biotesting. The synthetic availability of these natural biaryls, their precursors, and their unnatural analogs permitted a broader investigation of the antiplasmodial activities of these interesting biaryls.

12822907
Carmona D, Saez J, Granados H, Perez E, Blair S, Angulo A, Figadere B
Antiprotozoal 6-substituted-5,6-dihydro-alpha-pyrones from Raimondia cf. monoica.
Nat Prod Res. 2003 Aug;17(4):275-80.
Dichloromethane extracts of both the roots and the leaves of Raimondia cf. monoica showed in vitro antiplasmodial and leishmanicidal activities against Plasmodium falciparum and Leishmania panamensis,

respectively. Three 6-substituted 5,6-dihydro-2H-pyran-2-ones were isolated. (1) and (2) were identified as (6S)-(5'-oxohepten-1'E,3'E-dienyl)-5,6-dihydro-2H-pyran-2-one (1) and (6R)-(5'-oxohepten-1'Z,3'E-dienyl)-5,6-dihydro-2H-pyran-2-one (2), respectively. (-)-Arentilactone (3) was also isolated. The structure of the new compound (1) was determined by spectroscopic methods; additional spectroscopic data for (2) are reported for the first time.

16254833
Chan KL, Choo CY, Abdullah NR
Semisynthetic 15-O-acyl- and 1,15-di-O-acyleurycomanones from Eurycoma longifolia as potential antimalarials.
Planta Med. 2005 Oct;71(10):967-9.
Among the quassinoids isolated from Eurycoma longifolia Jack, eurycomanone was identified as the most potent and toxic inhibitor of the chloroquine-resistant Gombak A isolate of Plasmodium falciparum. Several diacylated derivatives of eurycomanone, 1,15-di-O-isovaleryleurycomanone, 1,15-di-O-(3,3-dimethylacryloyl)- eurycomanone and 1,15-di-O-benzoyleurycomanone were synthesized by direct acylation with the respective acid chlorides. The monoacylated 15-O-isovaleryleurycomanone was synthesized by selective protection of the other hydroxy groups of eurycomanone with trimethylsilyl trifluoromethanesulphonate to enable the exclusive acylation of its C-15 hydroxy group. This was followed by the removal of the protecting groups with citric acid. The diacylated eurycomanones exhibited lower antiplasmodial activity against the Gombak A isolates and lower toxicity in the brine shrimp assay when compared to eurycomanone. In contrast, the monoacylated derivative displayed comparable antiplasmodial potency to eurycomanone, but its toxicity was reduced. Thus, preliminary studies of the synthesized acylated eurycomanones have shown that acylation only at the C-15 hydroxy group may be worthy of further antimalarial investigation.

15138004
Chan KL, Choo CY, Abdullah NR, Ismail Z
Antiplasmodial studies of Eurycoma longifolia Jack using the lactate dehydrogenase assay of Plasmodium falciparum.
J Ethnopharmacol. 2004 Jun;92(2-3):223-7.
The roots of Eurycoma longifolia Jack have been used as traditional medicine to treat malaria. A systematic bioactivity-guided fractionation of this plant was conducted involving the determination of the effect of its various extracts and their chemical constituents on the lactate dehydrogenase activity of in vitro chloroquine-resistant Gombak A isolate and chloroquine-sensitive D10 strain of Plasmodium falciparum parasites. Their antiplasmodial activity was also compared with their known in vitro cytotoxicity against KB cells. Four quassinoids, eurycomanone (1), 13,21-dihydroeurycomanone (3), 13 alpha(21)-epoxyeurycomanone (4), eurycomalactone (6) and an alkaloid, 9-methoxycanthin-6-one (7), displayed higher antiplasmodial activity against Gombak A isolate but were less active against the D10 strain when compared with chloroquine. Amongst the compounds tested, 1 and 3 showed higher selectivity indices obtained for the cytotoxicity to antiplasmodial activity ratio than 14,15 beta-dihydroxyklaineanone (2), eurycomanol (5), 6 and 7.

16213121
Chukwujekwu JC, Smith P, Coombes PH, Mulholland DA, van Staden J
Antiplasmodial diterpenoid from the leaves of Hyptis suaveolens.
J Ethnopharmacol. 2005 Nov 14;102(2):295-7. Epub 2005 Oct 5.
Bioactivity-guided fractionation of the petroleum ether extract of the leaves of Hyptis suaveolens, widely used in Traditional Medicine, has led to the isolation of an abietane-type diterpenoid endoperoxide, 13 alpha-epi-dioxiabiet-8(14)-en-18-ol, displaying high antiplasmodial activity (IC(50) 0.1 microg/ml).

15507366
Cimanga RK, Tona L, Luyindula N, Mesia K, Lusakibanza M, Musuamba CT, Apers S, De Bruyne T, Van Miert S, Hermans N, Totte J, Pieters L, Vlietinck AJ
In vitro antiplasmodial activity of callus culture extracts and fractions from fresh apical stems of Phyllanthus niruri L. (Euphorbiaceae): part 2.
J Ethnopharmacol. 2004 Dec;95(2-3):399-404.
The ethanolic extracts from fresh apical stems of Phyllanthus niruri L. (Euphorbiaceae) cultured on Murashige and Skoog (MS) medium supplemented with IBA/BAP/Coco nucifera L. milk for 1, 2, 4 and 6 months were phytochemically and biologically investigated and compared with intact plant part and whole plant extracts. Results from the in vitro antiplasmodial testing indicated that the EtOH extract of a 1-month-old callus culture (IC(50) = 16.3 +/- 2.5 microg/ml) exhibited a higher activity than the ethanolic extracts of the fresh apical stem (IC(50) = 18.2 +/- 2.4 microg/ml) and callus cultures of 2-, 4- and 6-months-old (25 microg/ml < IC(50) < 40 microg/ml). These activities were however lower than that displayed by the ethanolic extract of the whole plant (IC(50) < 3 microg/ml). The EtOH extract of 1-month-old callus culture (the most

active) was fractionated with solvents of different polarities. Its CH(2)Cl(2) fraction rich in terpenic constituents (IC(50) = 9.2 +/- 3.4 microg/ml) exhibited a higher antiplasmodial activity than its isoamylic alcohol fraction obtained at pH 2-3 (IC(50) = 25.6 +/- 2.3 microg/ml) rich in flavonoids. The activity of these two fractions was lower than that displayed by the same fractions from the whole plant (2 microg/ml < IC(50) < 3 microg/ml). Alkaloidic fractions from the whole plant and 1-month-old callus culture of fresh apical stem were considered as inactive (IC(50) > 100 microg/ml).

14531022
Clarkson C, Campbell WE, Smith P
In vitro antiplasmodial activity of abietane and totarane diterpenes isolated from Harpagophytum procumbens (devil's claw).
Planta Med. 2003 Aug;69(8):720-4.
The development of drug resistance and resurgence of malaria has highlighted the need for new chemically diverse antimalarial drugs. This study investigates Harpagophytum procumbens DC. as a source of antiplasmodial hit compounds. The roots of wild harvested plants as well as the aerial sections, seeds and roots of cultivated H. procumbens were evaluated for in vitro antiplasmodial activity. Bioassay-guided fractionation of the petroleum ether root extract yielded two diterpenes, (+)-8,11,13-totaratriene-12,13-diol (1) and (+)-8,11,13-abietatrien-12-ol (2). Compounds 1 and 2 displayed significant (IC50 < 1 microg/mL) in vitro antiplasmodial activity against a chloroquine-resistant (K1) and -sensitive (D10) strain of Plasmodium falciparum, and low cytotoxicity (SI > 65) against two mammalian cell lines (CHO and HepG2). It was found that 1 and 2 did not modify the erythrocyte shape, which in conjunction with the cytotoxicity results, indicates selective antiplasmodial activity.

15137999
Clarkson C, Maharaj VJ, Crouch NR, Grace OM, Pillay P, Matsabisa MG, Bhagwandin N, Smith PJ, Folb PI
In vitro antiplasmodial activity of medicinal plants native to or naturalised in South Africa.
J Ethnopharmacol. 2004 Jun;92(2-3):177-91.
The increasing prevalence and distribution of malaria has been attributed to a number of factors, one of them being the emergence and spread of drug resistant parasites. Efforts are now being directed towards the discovery and development of new chemically diverse antimalarial agents. The present study reports on the in vitro antiplasmodial activity of 134 plant taxa native to or naturalised in South Africa, representing 54 families, which were selected semi-quantitatively using weighted criteria. The plant extracts were tested for in vitro activity against a Plasmodium falciparum strain D10 using the parasite lactate dehydrogenase (pLDH) assay. Of the 134 species assayed, 49% showed promising antiplasmodial activity (IC(50)< or = 10 microg/ml), while 17% were found to be highly active (IC(50)< or = 5 microg/ml). Several plant species and genera were shown for the first time to possess in vitro antiplasmodial activity. These results support a rational rather than random approach to the selection of antiplasmodial screening candidates, and identify a number of promising taxa for further investigation as plant-based antimalarial agents.

13129578
Clarkson C, Musonda CC, Chibale K, Campbell WE, Smith P
Synthesis of totarol amino alcohol derivatives and their antiplasmodial activity and cytotoxicity.
Bioorg Med Chem. 2003 Oct 1;11(20):4417-22.
The previously unknown antiplasmodial activity of the plant derived natural product totarol is reported. Novel beta-amino alcohol derivatives based on this natural product were designed, synthesised and evaluated for in vitro antiplasmodial activity and cytotoxicity. These derivatives showed antiplasmodial IC50 values in the range of 0.6-3.0 microM and were equally active against a chloroquine-sensitive and resistant strain of Plasmodium falciparum, while showing little cytotoxicity against a mammalian cell line (CHO). In terms of lead development, two of the compounds based on substituted phenylpiperazine warrant further investigation as potential antiplasmodial leads. In addition to their selective antiplasmodial activity and lack of chloroquine cross-resistance, these compounds are structurally different to any of the available antimalarial drugs.

12865971
Copp BR, Kayser O, Brun R, Kiderlen AF
Antiparasitic activity of marine pyridoacridone alkaloids related to the ascididemins.
Planta Med. 2003 Jun;69(6):527-31.
A series of pyridoacridone alkaloids, including the marine alkaloid ascididemin were tested in vitro for antiparasitic activity against P. falciparum (K1, NF54), L. donovani, T. cruzi, T. b. rhodesiense and two mammalian cell lines (L6, RAW 264.7). Most compounds showed high antiplasmodial activity, moderate antileishmanial activity against both extra- and intracellular forms, and significant trypanocidal effects against T. cruzi and T. b. brucei. However, when tested against mammalian cell lines, most of the compounds were

also toxic for macrophage-like RAW 264.7 cells and skeletal muscle myoblast L6 cells. Correlations between molecular structures and antiparasitic activity are discussed in detail. Specific compounds are illustrated with emphasis on their potential as new antiparasitic drug leads.

15835725
Dalsgaard PW, Larsen TO, Christophersen C
Bioactive cyclic peptides from the psychrotolerant fungus Penicillium algidum.
J Antibiot (Tokyo). 2005 Feb;58(2):141-4.
A new cyclic nitropeptide, psychrophilin D (1), together with two known cyclic peptides, cycloaspeptide A (2) and cycloaspeptide D (3), were isolated from the psychrotolerant fungus Penicillium algidum using C18 flash chromatography, LH-20 Sephadex and preparative HPLC. The structure of psychrophilin D (1) was derived from mass spectrometric information, 1D and 2D NMR spectra and Marfey's method. The compounds were tested in antimicrobial, antiviral, anticancer and antiplasmodial assays. Psychrophilin D (1) exhibited a moderate activity (ID50 10.1 microg/ml) in the P388 murine leukaemia cell assay. Cycloaspeptide A (2) and D (3) exhibited moderate activity (IC50 3.5 and 4.7 microg/ml, respectively) against Plasmodium falciparum.

10831392
de Ferreira-da-Cruz M, Adami YL, da Espinola-Mendes E, Figueiredo MR, Daniel-Ribeiro CT
The intraperitoneal Plasmodium berghei-Pasteur infection of Swiss mice is not a system that is able to detect the antiplasmodial activity in the Pothomorphe plant extracts that are used as antimalarials in Brazilian endemic areas.
Exp Parasitol. 2000 Apr;94(4):243-7.
The antimalarial activity of the hexane and methanol extracts derived from the Brazilian plants Pothomorphe peltata and Pothomorphe umbellata-whose leaves are popularly employed in medicinal folk remedies for the treatment of malaria-was assessed through in vivo tests with the Peters method. The extracts were delivered to Plasmodium berghei-infected mice via the oral or the subcutaneous route. A suppressive effect on the parasitemia seemed to be evident when data regarding the intraperitoneal injection of Pothomorphe umbellata extracts were analyzed. However, a definitive conclusion on an effective antimalarial activity is not possible, as two distinct-"standard" and "slow"-patterns of parasitemia occurring at similar frequencies in both treated and untreated intraperitoneally infected mice were observed. Nevertheless, the existence of two distinct profiles of parasitemia was not clear among the animals that were infected via the intravenous route. These data indicate the need for further studies on the biological features of the host/parasite interaction in the intraperitoneally P. berghei-infected Swiss mice system to standardize the model and to improve its usefulness in the screening of antimalarial compounds.

15908216
de Mesquita ML, Grellier P, Blond A, Brouard JP, de Paula JE, Espindola LS, Mambu L
New ether diglycosides from Matayba guianensis with antiplasmodial activity.
Bioorg Med Chem. 2005 Jul 15;13(14):4499-506.
Four new ether diglycosides (1-4), named matayosides A-D, were isolated from the root bark of Matayba guianensis, a plant exhibiting in vitro antiplasmodial activity. They were identified as hexadecyl-[O-2,3,4-tri-O-acetyl-alpha-L-rhamnopyranosyl-(1-->2)]-6-O-palmi toyl-beta-D-glucopyranoside, hexadecyl-[O-2,3,4-tri-O-acetyl-alpha-L-rhamnopyranosyl-(1-->2)]-4,6-di-O- acetyl-beta-D-glucopyranoside, hexadecyl-[O-2,3,4-tri-O-acetyl-alpha-L-rhamnopyranosyl-(1-->2)]-3,6-di-O- acetyl-beta-D-glucopyranoside and hexadecyl-[O-2,3,4-tri-O-acetyl-alpha-L-rhamnopyranosyl-(1-->2)]-6-O-acety l-beta-D-glucopyranoside, respectively. Their structures were established using one- and two-dimensional NMR techniques, mass spectrometry (MS) and MS/MS experiments. The compounds were found to inhibit the growth of Plasmodium falciparum in vitro with IC50 values ranging from 2.5 to 8.9 microg/mL.

16256062
de Monbrison F, Maitrejean M, Latour C, Bugnazet F, Peyron F, Barron D, Picot S
In vitro antimalarial activity of flavonoid derivatives dehydrosilybin and 8-(1;1)-DMA-kaempferide.
Acta Trop. 2006 Jan;97(1):102-7. Epub 2005 Oct 26.
Multidrug-resistant Plasmodium falciparum strains are an increasing problem in endemic areas and are partly responsible for the worsening malaria situation around the world. New cheap and effective compounds active in combination with available drug in the field are urgently needed. The aim of this work was to explore the potential antiplasmodial effect of flavonoid derivatives on parasites growth in vitro. In vitro antiplasmodial activity of dehydrosilybin and 8-(1;1)-DMA-kaempferide has been evaluated by real time PCR for five P. falciparum strains. Both revealed significative antimalarial activity against the different strains. Since this drug family has been largely used and well-tolerated in humans, flavonoid derivatives could be in the near future associated with already available drugs in order to delay the spread of P. falciparum resistance.

12007706

Debenedetti S, Muschietti L, van Baren C, Clavin M, Broussalis A, Martino V, Houghton PJ, Warhurst D, Steele J
In vitro antiplasmodial activity of extracts of Argentinian plants.
J Ethnopharmacol. 2002 May;80(2-3):163-6.
Fifteen extracts from nine selected Argentine medicinal plants were tested for their antiplasmodial activity in vitro by assessing their ability to inhibit the uptake of [3H]-hypoxanthine into the Plasmodium falciparum K1 pyrimethamine/chloroquine resistant strain. The methanol extract of Satureja parvifolia showed good antiplasmodial activity (IC(50) 3 microg/ml). Inhibition of the growth of P. falciparum was also observed with aqueous extracts of Buddleja globosa and S. parvifolia.

12873511
del Olmo E, Armas MG, Ybarra M, Lopez JL, Oporto P, Gimenez A, Deharo E, San Feliciano A
The imidazo[2,1-a]isoindole system. A new skeletal basis for antiplasmodial compounds.
Bioorg Med Chem Lett. 2003 Aug 18;13(16):2769-72.
The in vitro antiplasmodial activity of some dihydrostilbenamides, phtalazinones, imidazo[2,1-a]isoindole and pyrimido[2,1-a]isoindole derivatives related to the natural dihydrostilbenoid isonotholaenic acid is reported. The evaluation was performed on cultures of F32 strain of Plasmodium falciparum and potent representative compounds were also evaluated in the ferriprotoporphyrin IX biomineralization inhibition test (FBIT). Compounds having the imidazo[2,1-a]isoindole skeleton were the most active and one compound of this group resulted to be as potent as chloroquine, but acting through a mechanism different that of the inhibition of heme biomineralization.

12624824
Dell'Agli M, Parapini S, Basilico N, Verotta L, Taramelli D, Berry C, Bosisio E
In vitro studies on the mechanism of action of two compounds with antiplasmodial activity: ellagic acid and 3,4,5-trimethoxyphenyl(6'-O-aalloyl)-beta-D-glucopyranoside.
Planta Med. 2003 Feb;69(2):162-4.
To investigate the mechanism of action of two antiplasmodial compounds, ellagic acid and 3,4,5-trimethoxyphenyl (6'-O-galloyl)-beta-D-glucopyranoside (TMPGG), we studied in vitro two metabolic reactions of intraerythrocytic parasites: the activity of recombinant plasmepsin II, one of the haemoglobin proteases, and the detoxification of haematin into beta-haematin. Both compounds inhibited plasmepsin II activity, but at concentrations ten-fold higher than those needed for inhibiting parasite growth. Moreover, ellagic acid inhibited the formation of beta-haematin, with an IC50 only 3-fold higher than that of chloroquine. These data suggest that the antiplasmodial activity of ellagic acid could be related to the inhibition of beta-haematin formation, whereas plasmepsin II does not represent the main target of the two compounds.

16509575
Desai PV, Patny A, Gut J, Rosenthal PJ, Tekwani B, Srivastava A, Avery M
Identification of novel parasitic cysteine protease inhibitors by use of virtual screening. 2. The available chemical directory.
J Med Chem. 2006 Mar 9;49(5):1576-84.
The incidence of parasitic infections such as malaria, leishmaniasis, and trypanosomiasis has been steadily increasing. Since the existing chemotherapy of these diseases suffers from lack of safe and effective drugs and/or the presence of widespread drug resistance, there is an urgent need for development of potent, mechanism-based antiparasitic agents against these diseases. Cysteine proteases have been established as valid targets for this purpose. The Available Chemical Directory consisting of nearly 355,000 compounds was screened in silico against the homology models of plasmodial cysteine proteases, falcipain-2, and falcipain-3, to identify structurally diverse non-peptide inhibitors. The study led to identification of 22 inhibitors of parasitic cysteine proteases out of which 18 compounds were active against falcipain-2 and falcipain-3. Eight compounds exhibited dual activity against both enzymes. Additionally, four compounds were found to inhibit L. donovani cysteine protease. While one of the cysteine protease inhibitors also exhibited in vitro antiplasmodial activity with an IC50 value of 9.5 microM, others did not show noticeable antiplasmodial activity up to 20 microM. A model identifying important pharmacophoric features common to the structurally diverse falcipain-2 inhibitors has also been developed. Very few potent non-peptide inhibitors of the parasitic cysteine proteases have been reported so far, and identification of these novel and chemically diverse inhibitors should provide leads to be optimized into candidates to treat protozoal infections.

12020924
do Ceu de Madureira M, Paula Martins A, Gomes M, Paiva J, Proenca da Cunha A, do Rosario V
Antimalarial activity of medicinal plants used in traditional medicine in S. Tome and Principe islands.
J Ethnopharmacol. 2002 Jun;81(1):23-9.
The present study investigates the antimalarial activity of 13 medicinal plants used in traditional medicine in S. Tome and Principe (STP) islands in the Gulf of Guinea, aiming at identifying the most effective plants for

further research. Fieldwork was carried out with the collaboration of 37 traditional healers from both islands, during an ethnobotanical study, which was conducted from 1993 to 1999. Our results indicate that the traditional healers in STP use several medicinal plants against fever and/or 'malaria' which reveal strong antiparasitic activity in vitro: four of the plant extracts have evident antiplasmodial activity against chloroquine resistant Plasmodium falciparum, with IC(50) values

15022164
Duker-Eshun G, Jaroszewski JW, Asomaning WA, Oppong-Boachie F, Brogger Christensen S
Antiplasmodial constituents of Cajanus cajan.
Phytother Res. 2004 Feb;18(2):128-30.
Bioactivity-guided fractionation of extracts of roots and leaves of Cajanus cajan afforded 8 compounds: betulinic acid, biochanin A, cajanol, genistein and 2'-hydroxygenistein, longistylin A and C, and pinostrobin. The two stilbenes, longistylin A and C, and betulinic acid showed a moderately high in vitro activity against the chloroquine-sensitive Plasmodium falciparum strain 3D7.

12143001
Duker-Eshun G, Jaroszewski JW, Asomaning WA, Oppong-Boachie F, Olsen CE, Christensen SB
Antiplasmodial activity of labdanes from Aframomum latifolium and Aframomum sceptrum.
Planta Med. 2002 Jul;68(7):642-4.
Bioguided fractionation of extracts of Aframomum latifolium and A. sceptrum (Zingiberaceae) resulted in isolation of (+)-(S)-nerolidol and seven labdanes, coronarin B, galanal A and B, galanolactone, (E)-8beta,17-epoxylabd-12-ene-15,16-dial, (+)-(E)-labda-8(17), 12-diene-15,16-dial and its diethyl acetal, the latter being presumably an isolation artefact. The labdanes show a modest in vitro activity against a chloroquine-sensitive Plasmodium falciparum strain.

11937508
Efron L, Dagan A, Gaidukov L, Ginsburg H, Mor A
Direct interaction of dermaseptin S4 aminoheptanoyl derivative with intraerythrocytic malaria parasite leading to increased specific antiparasitic activity in culture.
J Biol Chem. 2002 Jul 5;277(27):24067-72. Epub 2002 Apr 5.
Antiplasmodial activity of the dermaseptin S4 derivative K(4)S4(1-13) (P) was shown to be mediated by lysis of the host cells. To identify antiplasmodial peptides with enhanced selectivity, we produced and screened new derivatives based on P and singled out the aminoheptanoylated peptide (NC7-P) for its improved antiplasmodial properties. Compared with P, NC7-P displayed both increased antiparasitic efficiency and reduced hemolysis, including against infected cells. Antiplasmodial activity of P and its derivative was time-dependent and irreversible, implying a cytotoxic effect. But, whereas the dose dependence of growth inhibition and hemolysis of infected cells overlapped when treated with P, NC7-P exerted more than 50% growth inhibition at peptide concentrations that did not cause hemolysis. Noticeably, NC7-P but not P, dissipated the parasite plasma membrane potential and caused depletion of intraparasite potassium at nonhemolytic conditions. Confocal microscopy analysis of infected cells localized the rhodaminated derivative in association with parasite membranes and intraerythrocytic tubulovesicular structures, whereas in normal cells, the peptide localized exclusively at the plasma membrane. Overall, the data demonstrate that antimicrobial peptides can be engineered to act specifically on the membrane of intracellular parasites and support a mechanism whereby NC7-P crosses the host cell plasma membrane and disrupts the parasite membrane(s).

10649984
Egan TJ, Hunter R, Kaschula CH, Marques HM, Misplon A, Walden J
Structure-function relationships in aminoquinolines: effect of amino and chloro groups on quinoline-hematin complex formation, inhibition of beta-hematin formation, and antiplasmodial activity.
J Med Chem. 2000 Jan 27;43(2):283-91.
Comparison of 19 aminoquinolines supports the hypothesis that chloroquine and related antimalarials act by complexing ferriprotoporphyrin IX (Fe(III)PPIX), inhibiting its conversion to beta-hematin (hemozoin) and hence its detoxification. The study suggests that a basic amino side chain is also essential for antiplasmodial activity. 2- And 4-aminoquinolines are unique in their strong affinity for Fe(III)PPIX, and attachment of side chains to the amino group has relatively little influence on the strength of complex formation. Association with Fe(III)PPIX is necessary, but not sufficient, for inhibiting beta-hematin formation. Presence of a 7-chloro group in the 4-aminoquinoline ring is a requirement for beta-hematin inhibitory activity, and this is also unaffected by side chains attached to the amino group. In turn, beta-hematin inhibitory activity is necessary, but not sufficient, for antiplasmodial activity as the presence of an aminoalkyl group attached to the 4-amino-7-chloroquinoline template is essential for strong activity. We thus propose that the 4-aminoquinoline nucleus of chloroquine and related antimalarials is responsible for complexing Fe(III)PPIX, the 7-chloro group is

required for inhibition of beta-hematin formation, and the basic amino side chain is required for drug accumulation in the food vacuole of the parasite.

10363837
El Tahir A, Satti GM, Khalid SA
Antiplasmodial activity of selected Sudanese medicinal plants with emphasis on Maytenus senegalensis (Lam.) Exell.
J Ethnopharmacol. 1999 Mar;64(3):227-33.
The antiplasmodial activity of plant extracts related to four families was tested on chloroquine sensitive strain 3D7 and chloroquine resistant strain Dd2 of Plasmodium falciparum. The methanolic extract of Harrisonia abyssinica (Simaroubaceae) inhibited Dd2 with IC50 value of 4.7 microg/ml, while in 3D7, the IC50 value was 10 microg/ml. Most of the plants from the family Meliaceae showed highly potent antiplasmodial activity against the two tested strains. Khaya senegalensis, Azadirachta indica and Trichilia emetica showed IC50 values less than 5 microg/ml. The methanolic extract of Annona squamosa (Annonaceae) leaves showed high antiplasmodial activity with IC50 values of 2 and 30 microg/ml on 3D7 and Dd2, respectively. While stem bark showed moderate activity with IC50 values of 8.5 and 120 microg/ml on Dd2. Maytenus senegalensis (Celastraceae) possessed IC50 values of 3.9 on 3D7, 10 microg/ml on Dd2 and had no effect on lymphocyte proliferation even at the highest tested concentration; the IC50 was greater than 100 microg/ml. Liquid-liquid separation of the methanolic extract of M. senegalensis revealed that the dichloromethane extract possessed an IC50 value of only 2.1 microg/ml. Column fractionation of dichloromethane extract gave four fractions and fraction two showed an IC50 value of 0.5 microg/ml. Preliminary phytochemical analysis of dichloromethane fraction revealed terpenoids and traces of phenolic principles but no alkaloid, tannins or flavonoids were detected.

10479756
El-Tahir A, Satti GM, Khalid SA
Antiplasmodial activity of selected sudanese medicinal plants with emphasis on Acacia nilotica.
Phytother Res. 1999 Sep;13(6):474-8.
Twenty-two plant organs from eleven plants comprising five families were extracted and screened for antiplasmodial activity in vitro against Plasmodium falciparum 3D7 (chloroquine sensitive) and Dd2 (chloroquine resistant and pyrimethamine sensitive). Fifty nine percent of plant extracts from 22 extracts exerted activity on P. falciparum strain 3D7 with an IC(50) less than 50 microg/mL, whereas 43% of plant extracts showed an IC(50) value within 50 microg/mL on Dd2 strains. Plant extracts from Gardenia lutea, Haplophyllum tuberculatum, Cassia tora, Acacia nilotica and Aristolochia bracteolata possessed IC(50) values less than 5 microg/mL on both tested strains. Bioassay guided fractionation of A. nilotica revealed that the ethyl acetate extract possessed the highest activity (IC(50) = 1.5 microg/mL). Fraction 2 (R(f) = 0.75) prepared by preparative chromatography showed the highest activity on P. falciparum (IC(50) = 1.7 microg/mL). Phytochemical analysis indicated that the most active phase contained terpenoids and tannins and was devoid of alkaloids and saponins. The effect of plant extracts on lymphocyte proliferation showed low toxicity to the human cells. This plant has been subjected to long term clinical trials in folk medicine and is a promising plant.

10705750
Federici E, Palazzino G, Nicoletti M, Galeffi C
Antiplasmodial activity of the alkaloids of Peschiera fuchsiaefolia.
Planta Med. 2000 Feb;66(1):93-5.
The tertiary and quaternary alkaloids isolated from the stem bark, root bark and seeds of Peschiera fuchsiaefolia are reported. The tertiary alkaloid crude extract from the stem bark was tested in vitro against Plasmodium falciparum on the basis of the antimalarial use of the plant. It showed good activity against both the D6 strain (IC50 = 495 ng/ml) and chloroquine-resistant W2 strain (IC50 = 817 ng/ml) and voacamine was the most active of the tested alkaloids (IC50 = 238 ng/ml for D6 and 290 ng/ml for W2). The tertiary alkaloid crude extract from the root bark of the same plant is more active than voacamine (IC50 = 179 ng/ml for D6 and 282 ng/ml for W2 strain), and is particularly rich in dimeric alkaloids (0.22% of the vegetable material).

16443341
Fiot J, Sanon S, Azas N, Mahiou V, Jansen O, Angenot L, Balansard G, Ollivier E
Phytochemical and pharmacological study of roots and leaves of Guiera senegalensis J.F. Gmel (Combretaceae).
J Ethnopharmacol. 2006 Jan 26;.
The chemical composition of total alkaloids from leaves and roots of Guiera senegalensis was investigated. Three beta-carboline alkaloids were purified: in addition to harman and tetrahydroharman, known in roots and leaves, harmalan (dihydroharman) was isolated for the first time from roots of Guiera senegalensis. Guieranone A, a naphthyl butenone, was also purified from leaves and roots. The in vitro antiplasmodial

activity and the cytotoxicity of extracts and pure compounds were evaluated. Each total alkaloid extract and beta-carboline alkaloids presented an interesting antiplasmodial activity associated with a low cytotoxicity. Harmalan was less active than harman and tetrahydroharman. Guieranone A showed a strong antiplasmodial activity associated with a high cytotoxicity toward human monocytes. Its cytotoxicity was performed against two cancer cell lines and normal skin fibroblasts in order to study its anticancer potential: guieranone A presented a strong cytotoxicity against each cell strains. Finally, we evaluated the potent synergistic antimalarial interaction between Guiera senegalensis and two plants commonly associated in traditional remedies: Mitragyna inermis and Pavetta crassipes. Three associations evaluated were additive. A synergistic effect was shown between total alkaloids extracted from leaves of Guiera senegalensis and those of Mitragyna inermis. This result justified the traditional use of the plants in combination to treat malaria.

15533296
Fischer DC, de Amorim Gualda NC, Bachiega D, Carvalho CS, Lupo FN, Bonotto SV, Alves Mde O, Yogi A, Santi SM, Avila PE, Kirchgatter K, Moreno PR
In vitro screening for antiplasmodial activity of isoquinoline alkaloids from Brazilian plant species.
Acta Trop. 2004 Nov-Dec;92(3):261-6.
In the search for new antimalarial agents, nine Brazilian plant species were selected, from the Annonaceae (6), Menispermaceae (2) and Siparunaceae (1) families naturally occurring at the cerrado and Atlantic rainforest regions, in order to investigate their in vitro antiplasmodial activity. The ethanol and the alkaloid extracts were tested against K1, chloroquine-resistant, and Palo Alto, chloroquine-sensitive, strains of Plasmodium falciparum. The majority of the alkaloid extracts were more active than the ethanol ones, with IC(50) ranging 0.3-8.2 microg/mL. The crude Guatteria australis alkaloids were the most active against K1 with an IC(50) = 0.3 microg/mL. The most promising total alkaloid fractions for further bioguided isolation are those with the IC(50) < or = 5 microg/mL: G. australis, Cissampelos ovalifolia and Duguetia lanceolata.

15504827
Fivelman QL, Adagu IS, Warhurst DC
Modified fixed-ratio isobologram method for studying in vitro interactions between atovaquone and proguanil or dihydroartemisinin against drug-resistant strains of Plasmodium falciparum.
Antimicrob Agents Chemother. 2004 Nov;48(11):4097-102.
A modified fixed-ratio isobologram method for studying the in vitro interactions between antiplasmodial drugs is described. This method was used to examine the interactions between atovaquone, proguanil, and dihydroartemisinin. The interaction between atovaquone and proguanil was synergistic against atovaquone-sensitive strains K1 and T996; however, there was a loss of synergy against atovaquone-resistant strain NGATV01 isolated after Malarone (the combination of atovaquone and proguanil) treatment failure. While the interaction between atovaquone and dihydroartemisinin was indifferent against isolate NGATV01, the interaction displayed indifference tending toward antagonism against the atovaquone-sensitive strains tested. The relevance of in vitro interactions to in vivo treatment is discussed.

11078887
Florent I, Mouray E, Dali Ali F, Drobecq H, Girault S, Schrevel J, Sergheraert C, Grellier P
Cloning of Plasmodium falciparum protein disulfide isomerase homologue by affinity purification using the antiplasmodial inhibitor 1,4-bis[3-[N-(cyclohexyl methyl)amino]propyl]piperazine..
FEBS Lett. 2000 Nov 10;484(3):246-52.
A series of 10 1,4-bis(3-aminopropyl)piperazine compounds was found to display antiplasmodial activity with 50% growth inhibition between 30 and 250 nM, on three Plasmodium falciparum strains differently sensitive to chloroquine. By affinity chromatography using one of these compounds, a 52-kDa protein was isolated from P. falciparum, microsequenced and cloned. It corresponded to a single copy gene encoding a 453 amino acid protein displaying the typical features of protein disulfide isomerases, a thiol metabolizing enzyme belonging to the thiol: disulfide oxidoreductase superfamily, which was not previously described in malarial species.

10382608
Francois G, Steenackers T, Assi LA, Steglich W, Lamottke K, Holenz J, Bringmann G
Vismione H and structurally related anthranoid compounds of natural and synthetic origin as promising drugs against the human malaria parasite Plasmodium falciparum: structure-activity relationships.
Parasitol Res. 1999 Jul;85(7):582-8.
Natural and synthetic anthranoid compounds were subjected to an evaluation against asexual erythrocytic stages of the human malaria parasite Plasmodium falciparum in vitro. Stimulated by the good activities of Vismia guineensis extracts, a more detailed investigation of the active principles revealed the pre-nylated preanthraquinone vismione H (1) to be a potent antimalarial [50% growth-inhibitory concentration (IC50) 0.088 microg/ml]. On the basis of this finding a series of chemically related phlegmacins (2-5), flavomannins

(6-8), and rufoolivacins (9-11) isolated from several species of Cortinarius, a genus of higher fungi, and 5 synthetic vismione-like anthranoids (12-16) were evaluated as well. Although these compounds displayed weaker antiplasmodial effects than did vismione H (1) itself, considerable levels of activity were obtained with phlegmacin B1 (2), flavomannin-6,6'-di-O-methyl ether A1 (6), trans-4-hydroxy-flavomannin-6,6'-di-O-methyl ether A (8), and rufoolivacin B (10). Initial preconditions for activity within the vismiones and related anthranoids were established.

14765299
Frederich M, Cristino A, Choi YH, Verpoorte R, Tits M, Angenot L, Prost E, Nuzillard JM, Zeches-Hanrot M
Chrysopentamine, an antiplasmodial anhydronium base from Strychnos usambarensis leaves.
Planta Med. 2004 Jan;70(1):72-6.
A new derivative of strychnopentamine was isolated from the leaves of Strychnos usambarensis. This compound, named chrysopentamine, was identified by detailed spectroscopic methods (UV, IR, HR-ESI-MS, 1D and 2D NMR). Chrysopentamine presented an original hydroxy substitution on C-14 and an aromatization of the ring D of strychnopentamine leading to anhydronium base properties and exhibited strong antiplasmodial properties (IC (50) less than 1 microM).

11170658
Frederich M, De Pauw M, Prosperi C, Tits M, Brandt V, Penelle J, Hayette M, DeMol P, Angenot L
Strychnogucines A and B, two new antiplasmodial bisindole alkaloids from Strychnos icaja.
J Nat Prod. 2001 Jan;64(1):12-6.
A reinvestigation of Strychnos icaja roots has resulted in the isolation of two tertiary quasi-symmetric bisindole alkaloids named strychnogucines A (1) and B (2). Their structures were identified by means of spectroscopic data interpretation. Compound 2 was highly active in vitro and compound 1 moderately active against four strains of Plasmodium falciparum. Strychnogucine B (2) was more active against a chloroquine-resistant strain than against a chloroquine-sensitive one (best CI(50), 80 nM against the W2 strain). In addition, this compound showed a selective antiplasmodial activity with 25-180 times greater toxicity toward P. falciparum, relative to cultured human cancer cells (KB) or human fibroblasts (WI38).

10821054
Frederich M, De Pauw MC, Llabres G, Tits M, Hayette MP, Brandt V, Penelle J, De Mol P, Angenot L
New antimalarial and cytotoxic sungucine derivatives from Strychnos icaja roots.
Planta Med. 2000 Apr;66(3):262-9.
Reinvestigation of Strychnos icaja Baillon resulted in the isolation of vomicine, isostrychnine and of three new sungucine derivatives, named isosungucine (8), 18-hydroxy-sungucine (9) and 18-hydroxy-isosungucine (10). They were identified by detailed spectroscopic methods. The complete 1H- and 13C-NMR study of sungucine was also realized. Some of these compounds were highly active against Plasmodium falciparum in vitro and more particularly against the chloroquine-resistant strain. Compound 10 showed a selective antiplasmodial activity, with > 100-fold greater toxicity towards Plasmodium falciparum, relative to cultured human cancer cells (KB and HeLa lines) or fibroblasts (WI38).

11509972
Frederich M, Hayette MP, Tits M, De Mol P, Angenot L
Reversal of chloroquine and mefloquine resistance in Plasmodium falciparum by the two monoindole alkaloids, icajine and isoretuline.
Planta Med. 2001 Aug;67(6):523-7.
Eight naturally occurring monoindole alkaloids were evaluated in vitro for their ability to inhibit Plasmodium falciparum growth and, in drug combination, to reverse the resistance of a chloroquine-resistant strain of Plasmodium falciparum. None of these indole alkaloids has significant intrinsic antiplasmodial activity (IC(50) > 10 microM or 5 microg/ml). Nevertheless, three alkaloids (icajine, isoretuline and strychnobrasiline) did reverse chloroquine resistance at concentrations between 2.5 and 25 microg/ml (IF of 12.82 for isoretuline on W2 strain). The Interaction Factor (IF) equals 2, < 2, or > 2 for additive, antagonistic or synergistic effects of alkaloids on chloroquine inhibition, respectively. Icajine and isoretuline were also assessed in vitro for their mefloquine potentiating activity on a mefloquine-resistant strain of Plasmodium falciparum. Only icajine proved to be synergistic with mefloquine (IF = 15.38).

12398531
Frederich M, Jacquier MJ, Thepenier P, De Mol P, Tits M, Philippe G, Delaude C, Angenot L, Zeches-Hanrot M
Antiplasmodial activity of alkaloids from various strychnos species.
J Nat Prod. 2002 Oct;65(10):1381-6.

The in vitro antiplasmodial activities of 69 alkaloids from various Strychnos species were evaluated against chloroquine-resistant and chloroquine-sensitive lines of Plasmodium falciparum. The compounds, comprising mainly indolomonoterpenoid alkaloids, exhibited a wide range of biological potencies in the antiplasmodial assays. The most active alkaloids were also tested for cytotoxicity against HCT-116 colon cancer cells to determine their antiplasmodial selectivity. As a result of these studies, structure-activity relationships for these alkaloids have begun to emerge. Alkaloids presenting four types of bisindole skeleton exhibited potent and selective activities against Plasmodium. They were sungucine-type (IC(50) values ranging from 80 nM to 10 microM), longicaudatine-type (IC(50) values ranging from 0.5 to 10 microM), matopensine-type (IC(50) values ranging from 150 nM to 10 microM), and usambarine-type alkaloids. Within the last structural type, isostrychnopentamine (49) and ochrolifuanine A (46) were found to be active against chloroquine-sensitive and -resistant strains (IC(50) values of 100-150 and 100-500 nM, respectively), and dihydrousambarensine (51) exhibited a 30-fold higher activity against the chloroquine-resistant strain (IC(50) = 32 nM) than against the chloroquine-sensitive one.

15229803
Frederich M, Tits M, Goffin E, Philippe G, Grellier P, De Mol P, Hayette MP, Angenot L
In vitro and in vivo antimalarial properties of isostrychnopentamine, an indolomonoterpenic alkaloid from Strychnos usambarensis.
Planta Med. 2004 Jun;70(6):520-5.
Isostrychnopentamine (ISP) is an asymmetric indolomonoterpenic alkaloid isolated from the leaves of Strychnos usambarensis. The in vitro antiplasmodial activities against five Plasmodium falciparum cell lines were evaluated: ISP possessed an in vitro IC (50) near 0.1 microM against all P. falciparum cell lines tested (chloroquine-resistant and chloroquine-sensitive lines) and showed antiplasmodial selectivity compared to cytotoxicity on human cell lines. The stage-dependent susceptibility to a short exposure of ISP was then investigated. The ring stage was shown to be the most sensitive one, but all stages were affected by ISP treatment. By means of fluorescence microscopy, it was shown that ISP was not accumulated inside the food vacuole of the parasite. Finally, the in vivo antimalarial activities against the P. berghei NK173 and P. vinckei petteri murine strains were determined. The ED (50) in vivo was about 30 mg/kg/day by the intraperitoneal route (after 4 days treatment).

15824094
Frolich S, Schubert C, Bienzle U, Jenett-Siems K
In vitro antiplasmodial activity of prenylated chalcone derivatives of hops (Humulus lupulus) and their interaction with haemin.
J Antimicrob Chemother. 2005 Jun;55(6):883-7. Epub 2005 Apr 11.
OBJECTIVES: There is an urgent need to discover new antimalarials, due to the spread of chloroquine resistance and the limited number of available drugs. Chalcones are one of the classes of natural products that are known to possess antiplasmodial properties. Therefore, the in vitro antiplasmodial activity of the main hop chalcone xanthohumol and seven derivatives was evaluated. In addition, the influence of the compounds on glutathione (GSH)-dependent haemin degradation was analysed to determine its contribution to the antimalarial effect of chalcones. METHODS: In vitro antiplasmodial activity was evaluated against the chloroquine-sensitive strain poW and the multiresistant clone Dd2 using a [(3)H]hypoxanthine-incorporation assay. Inhibition of GSH-dependent haemin degradation was analysed by a multiwell plate assay at 11 microM. RESULTS: Of the eight compounds tested, four possessed activity with IC(50) values

16453274
Frosch T, Schmitt M, Schenzel K, Faber JH, Bringmann G, Kiefer W, Popp J
In-vivo localization and identification of the antiplasmodial alkaloid dioncophylline A in the tropical liana Triphyophyllum peltatum by a combination of fluorescence, NIR FT Raman microscopy, and DFT calculations.
Biopolymers. 2006 Feb 1;.
Near Infrared Fourier Transform (NIR FT) micro Raman spectroscopy in combination with density functional theory (DFT) calculations has been applied for an in-vivo localization of the antiplasmodial naphthylisoquinoline alkaloid dioncophyl ine A (1) in the tropical liana Triphyophyllum peltatum. Fluorescence microscopy images suggest finding this active agent in 10 mum big inclusions located in the cortex of the stem or the beginning of the leaves. By means of spatially resolved FT Raman micro spectroscopy we could detect dioncophyl ine A (1) in these inclusions. FT Raman spectroscopy is an extremely selective tool capable to differentiate between various structurally similar naphthylisoquinoline alkaloids. With the help of DFT calculations we succeeded in assigning the differences found in the FT Raman spectra of the various naphthylisoquinolines to nuC=C vibrations of the naphthyl ring. The presented results are of relevance for the investigation and extraction of new antimalarial active agents. (c) 2006 Wiley Periodicals, Inc. Biopolymers, 2006.

16180813
Garzon SP, Rodriguez AD, Sanchez JA, Ortega-Barria E
Sesquiterpenoid metabolites with antiplasmodial activity from a Caribbean gorgonian coral, Eunicea sp.
J Nat Prod. 2005 Sep;68(9):1354-9.
A chemical investigation of the Caribbean gorgonian octocoral Eunicea sp. collected along the northwest coast of Puerto Rico has afforded seven new secondary metabolites, 1-7, belonging to several types of sesquiterpenes, including elemane, eudesmane, and germacrane types, along with the known steroidal glycoside 8. Some of the new metabolites, 4-7, carry an unusual ester side chain at the C-6 position. The structures of all compounds, including their relative stereochemistry, were determined by combined spectroscopic methods. The present compounds exhibited a significant inhibitory effect upon the growth of the malarial parasite Plasmodium falciparum.

15196005
Gelhaus C, Vicik R, Hilgenfeld R, Schmidt CL, Leippe M, Schirmeister T
Synthesis and antiplasmodial activity of a cysteine protease-inhibiting biotinylated aziridine-2,3-dicarboxylate.
Biol Chem. 2004 May;385(5):435-8.
Cysteine proteases have been implicated in a variety of processes essential for the survival and progression of the malarial parasite Plasmodium falciparum. Here, we synthesized a cysteine protease inhibitor that contains the electrophilic aziridine-2,3-dicarboxylic acid as the reactive agent and biotin as a targeting label. Diethyl ester and dibenzyl ester derivatives of the inhibitor were active against cathepsin L and the plasmodial protease falcipain 2, but only the latter displayed potent antiplasmodial activity against viable parasites. The morphological changes observed during the intraerythrocytic life stages of Plasmodium suggest that degradation of hemoglobin of the host cell is seriously affected, eventually leading to growth arrest and cell death of the parasites. After incubation of infected erythrocytes with the compound plasmodial proteins were captured, with the biotinyl group of the inhibitor serving as an affinity tag. Among these the cysteine proteases falcipain 2 and falcipain 3 were identified as potential target proteins of the compound as evidenced by tandem mass spectrometry. Apparently, the compound gets access to intracellular compartments and therein targets plasmodial cysteine proteases. Accordingly, the reagent described here appears to be a valuable template to develop cell-permeable, non-radioactive reagents that selectively target enzymes involved in pathogenicity of the parasite.

11356101
Girault S, Grellier P, Berecibar A, Maes L, Lemiere P, Mouray E, Davioud-Charvet E, Sergheraert C
Antiplasmodial activity and cytotoxicity of bis-, tris-, and tetraquinolines with linear or cyclic amino linkers.
J Med Chem. 2001 May 24;44(11):1658-65.
Bisquinoline heteroalkanediamines were structurally modified in order to study the effects of enhanced bulkiness and rigidity on both their activity on strains of Plasmodium falciparum expressing different degrees of chloroquine (CQ) resistance and their cytotoxicity toward mammalian cells. While cyclization yielded molecules of greater rigidity that were not more active than their linear counterparts, they were characterized by an absence of cytotoxicity. Alternatively, dimerization of these compounds led to tetraquinolines that are very potent for CQ-resistant strains and noncytotoxic.

12710020
Go ML
Novel antiplasmodial agents.
Med Res Rev. 2003 Jul;23(4):456-87.
The morbidity and mortality associated with malaria have spurred efforts to find novel antimalarial agents with improved potency and selectivity. Leads for agents continue to be obtained from natural sources (plants and microorganisms) and chemical syntheses. Screening of commercial or specialized databases have also yielded promising leads. The structural diversity of compounds with good (micromolar and lower) activity point to the considerable tolerance for different structural elements in the "antimalarial pharmacophore." It may also be a reflection of the varied targets present in the plasmodia. The challenge in malaria chemotherapy is to find safe and selective agents whose potencies will not be compromised by plasmodial resistance. Modification of potential leads should also aim at improving "drug-like" character, viz. to ensure acceptable oral bioavailability. A review of the literature shows that there is a growing trend towards the development of target-specific antimalarial agents (for example, agents inhibiting plasmodial farnesyl transferase, cyclin dependent kinases, proteases, choline transport). An increasing number of reports focus on the development of chemosensitizers, agents that are capable of reversing plasmodial resistance.

15328079
Go ML, Liu M, Wilairat P, Rosenthal PJ, Saliba KJ, Kirk K
Antiplasmodial chalcones inhibit sorbitol-induced hemolysis of Plasmodium falciparum-infected erythrocytes.

Antimicrob Agents Chemother. 2004 Sep;48(9):3241-5.
A series of alkoxylated and hydroxylated chalcones previously reported to have antiplasmodial activities in vitro were investigated for their effects on the new permeation pathways induced by the malaria parasite in the host erythrocyte membrane. Of 21 compounds with good antiplasmodial activities (50% inhibitory concentrations [IC(50)s], < or = 20 microM), 8 members were found to inhibit sorbitol-induced lysis of parasitized erythrocytes to a significant extent (< or = 40% of control values) at a concentration (10 microM) that was close to their antiplasmodial IC(50)s. Qualitative structure-activity analysis suggested that activity was governed to a greater extent by a substitution on ring B than on ring A of the chalcone template. Most of the active compounds had methoxy or dimethoxy groups on ring B. Considerable variety was permitted on ring A in terms of the electron-donating or -withdrawing property. Lipophilicity did not appear to be an important determinant for activity. Although they are not exceptionally potent as inhibitors (lowest IC(50), 1.9 microM), the chalcones compare favorably with other more potent inhibitors in terms of their selective toxicities against plasmodia and their neutral character.

10978215
Goclik E, Konig GM, Wright AD, Kaminsky R
Pelorol from the tropical marine sponge Dactylospongia elegans.
J Nat Prod. 2000 Aug;63(8):1150-2.
From the dichloromethane solubles of the tropical marine sponge Dactylospongia elegans, a new aromatic substituted sesquiterpene, pelorol (1), and the known sesquiterpene, ilimaquinone (2), were isolated. The structures of 1 and 2 were deduced from their spectroscopic data. The biological activities of compounds 1 and 2 were assessed in a variety of bioassays, and both compounds were found to have weak antitrypanosomal and antiplasmodial effects.

12094301
Goffin E, Ziemons E, De Mol P, de Madureira Mdo C, Martins AP, da Cunha AP, Philippe G, Tits M, Angenot L, Frederich M
In vitro antiplasmodial activity of Tithonia diversifolia and identification of its main active constituent: tagitinin C.
Planta Med. 2002 Jun;68(6):543-5.
The antimalarial properties of Tithonia diversifolia, an Asteraceae traditionally used to treat malaria, were investigated in vitro against three strains of Plasmodium falciparum. The ether extract from aerial parts of the plant collected in Sao Tome e Principe, demonstrated good antiplasmodial activity (IC 50 on FCA strain: 0.75 microg/ml). A bioassay guided fractionation of this extract led to the isolation of the known sesquiterpene lactone tagitinin C as an active component against Plasmodium (IC 50 on FCA strain: 0.33 microg/ml), but also possessing cytotoxic properties (IC 50 on HTC-116 cells: 0.706 microg/ml).

11556806
Grellier P, Sarlauskas J, Anusevicius Z, Maroziene A, Houee-Levin C, Schrevel J, Cenas N
Antiplasmodial activity of nitroaromatic and quinoidal compounds: redox potential vs. inhibition of erythrocyte glutathione reductase.
Arch Biochem Biophys. 2001 Sep 15;393(2):199-206.
Prooxidant nitroaromatic and quinoidal compounds possess antimalarial activity, which might be attributed either to their formation of reactive oxygen species or to their inhibition of antioxidant enzyme glutathione reductase (GR, EC 1.6.4.2). We have examined the activity in vitro against Plasmodium falciparum of 24 prooxidant compounds of different structure (nitrobenzenes, nitrofurans, quinones, 1,1'-dibenzyl-4,4'-bipyridinium, and methylene blue), which possess a broad range of single-electron reduction potentials (E(1)(7)) and erythrocyte glutathione reductase inhibition constants (K(i(GR))). For a series of homologous derivatives of 2-(5'-nitrofurylvinyl)quinoline-4-carbonic acid, the relationship between compound K(i(GR)) and concentration causing 50% parasite growth inhibition (IC(50)) was absent. For all the compounds examined in this study, the dependence of IC(50) on their K(i(GR)) was insignificant. In contrast, IC(50) decreased with an increase in E(1)(7) and positive electrostatic charge of aromatic part of molecule (Z): log IC(50) (microM) = -(0.9846 +/- 0.3525) - (7.2850 +/- 1.2340) E(1)(7) (V) - (1.1034 +/- 0.1832) Z (r(2) = 0.8015). The redox cycling activity of nitroaromatic and quinoidal compounds in ferredoxin:NADP(+) reductase-catalyzed reaction and the rate of oxyhemoglobin oxidation in lysed erythrocytes increased with an increase in their E(1)(7) value. Our findings imply that the antiplasmodial activity of nitroaromatic and quinoidal compounds is mainly influenced by their ability to form reactive oxygen species, and much less significantly by the GR inhibition.

15673723
Hatabu T, Takada T, Taguchi N, Suzuki M, Sato K, Kano S
Potent plasmodicidal activity of a heat-induced reformulation of deoxycholate-amphotericin B (Fungizone) against Plasmodium falciparum.

Antimicrob Agents Chemother. 2005 Feb;49(2):493-6.
The emergence and spread of drug-resistant Plasmodium falciparum continue to pose problems in malaria chemotherapy. Therefore, it is necessary to identify new antimalarial drugs and therapeutic strategies. In the present study, the activity of a heat-treated form of amphotericin B (HT-AMB) against P. falciparum was evaluated. The efficacy and toxicity of HT-AMB were also compared with those of the standard formulation (AMB). HT-AMB showed significant activity against a chloroquine-resistant strain (strain K-1) and a chloroquine-susceptible strain (strain FCR-3) in vitro. The 50% inhibitory concentrations of HT-AMB were 0.32 +/- 0.03 mug/ml for strain K-1 and 0.33 +/- 0.03 mug/ml for strain FCR-3. In the presence of 1.0 mug of HT-AMB per ml, only pyknotic parasites were observed after 24 h of incubation of early trophozoites (ring forms). However, when late trophozoites and schizonts were cultured with 1.0 mug of HT-AMB per ml, those forms multiplied to ring forms but the number of infected erythrocytes did not increase. These results indicate that HT-AMB possesses potent antiplasmodial activity and that the drug is more effective against the ring-form stage than against the late trophozoite and schizont stages. HT-AMB was observed to have little cytotoxic effect against a human liver cell line (Chang liver cells). In conclusion, the results suggest that HT-AMB has promising properties and merits further in vivo investigations as a treatment for falciparum malaria.

15673784
Hayward R, Saliba KJ, Kirk K
Mutations in pfmdr1 modulate the sensitivity of Plasmodium falciparum to the intrinsic antiplasmodial activity of verapamil.
Antimicrob Agents Chemother. 2005 Feb;49(2):840-2.
As well as having the ability to reverse chloroquine resistance in the human malaria parasite Plasmodium falciparum, verapamil has itself an innate antiplasmodial activity. We show here that mutations in Pgh1, the product of the malaria parasite's pfmdr1 gene, influence the parasite's susceptibility to the toxic effects of verapamil.

12094306
Hernandez-Medel Mdel R, Pereda-Miranda R
Cytotoxic anthraquinone derivatives from Picramnia antidesma.
Planta Med. 2002 Jun;68(6):556-8.
Activity-guided investigation of crude extracts prepared from the root bark of Picramnia antidesma, a medicinal plant long used for the treatment of malaria in tropical areas of the Americas, when tested on KB cells led to the isolation of a new compound, 10-epi-uveoside, from a cytotoxic fraction containing a rich mixture of anthrone glycosides. The antiplasmodial activity proved to be a result of the high levels of cytotoxicity displayed by the anthraquinone derivatives and therefore infusions from this crude drug lack the selectivity index needed to be an effective antimalarial agent.

11292242
Horgen FD, Edrada RA, de los Reyes G, Agcaoili F, Madulid DA, Wongpanich V, Angerhofer CK, Pezzuto JM, Soejarto DD, Farnsworth NR
Biological screening of rain forest plot trees from Palawan Island (Philippines).
Phytomedicine. 2001 Jan;8(1):71-81.
Study plots totaling 0.2 Ha were established in primary forest in the highlands of central Palawan Island, Philippines. Samples of various anatomical parts [typically leaf + twig (lf/tw), stem bark (sb), and root (rt)] were collected from all tree species represented within the plots by individuals having a diameter at breast height > or = 10 cm. In all, 211 distinct samples were obtained from 68 tree species, representing 35 families (not including samples from 4 indeterminate species). Methanol extracts of these samples were tested in in vitro antiplasmodial, brine shrimp toxicity, and cytotoxicity assays. The following samples showed an IC50 < or = 10 microg/mL against either chloroquine-sensitive or chloroquine-resistant clones of Plasmodium falciparum: Acronychia laurifolia (sb), Agathis celebica (lf/tw), Aglaia sp. 1 (sb), Aglaia sp. 2 (lf/tw, rt), Bhesa sp. 1 (rt), Cinnamomum griffithii (lf/tw), Croton leiophyllus (rt), Dysoxylum cauliflorum (rt), Garcinia macgregorii (sb), Lithocarpus sp. 1 (rt, sb), Meliosma pinnata ssp. macrophylla (lf/tw, rt), Myristica guatteriifolia (lf/tw), Ochrosia glomerata (rt, sb), Swintonia foxworthyi (lf/tw), Syzygium sp. 1 (rt), Turpinia pomifera (rt), and Xanthophyllum flavescens (sb). Secondly, those samples which displayed > or = 50% immobilization of brine shrimp at 100 microg/mL were: Acronychia laurifolia (lf/tw/fruit, rt, sb), Agathis celebica (lf/tw, sb), Aglaia sp. 1 (lf/tw), Alphonsea sp. 1 (rt), Ardisia iwahigensis (lf/tw), Arthrophyllum ahernianum (lf/tw, rt, sb), Castanopsis cf. evansii (rt), Cinnamomum griffithii (lf/tw, rt), Croton argyratus (lf/tw), C. leiophyllus (lf/tw, rt), Dysoxylum cauliflorum (fruit, lf/tw, rt), Euonymus javanicus (rt), Glochidion sp. 1 (rt), Polyosma sp. 1 (rt), Symplocos polyandra (rt), Timonius gammillii (sb), and Xanthophyllum flavescens (rt). Lastly, samples which exhibited an IC50 < or = 20 microg/mL against one or more of the cancer cell lines employed (LU1, KB, KB-V1, P-388, LNCaP, or ZR-75-1) include: Acronychia laurifolia (lf/tw/fruit, rt, sb), Aglaia sp. 1 (sb), Aglaia sp. 2 (rt), Alphonsea sp. 1 (rt), Ardisia iwahigensis (lf/tw, rt, sb), Astronia cumingiana (sb), Croton argyratus (lf/tw, rt, sb), C. leiophyllus (lf/tw, rt), Dimorphocalyx murina (lf/tw, rt, sb), Lithocarpus

caudatifolius (rt, sb), Litsea cf. sibuyanensis (rt), Syzygium cf. attenuatum (rt, sb), S. confertum (sb), Ternstroemia gitingensis (rt), and Ternstroemia sp. 1 (rt, sb).

10909272
Isaka M, Jaturapat A, Kladwang W, Punya J, Lertwerawat Y, Tanticharoen M, Thebtaranonth Y
Antiplasmodial compounds from the wood-decayed fungus Xylaria sp. BCC 1067.
Planta Med. 2000 Jun;66(5):473-5.
Bioassay-guided fractionation of the extract from the wood-decayed fungus Xylaria sp. BCC 1067 led to the isolation of five antiplasmodial compounds, (-)-depudecin, (+)-phaseolinone, (+)-phomenone, 19,20-epoxycytochalasin Q, and (E)-methyl 3-(4-methoxyphenoxy)propenoate. These structures were elucidated using spectroscopic methods, especially NMR analysis.

11842332
Jacquemond-Collet I, Benoit-Vical F, Valentin A, Stanislas E, Mallie M, Fouraste I
Antiplasmodial and cytotoxic activity of galipinine and other tetrahydroquinolines from Galipea officinalis.
Planta Med. 2002 Jan;68(1):68-9.
The antimalarial and toxicological properties of four tetrahydroquinoline alkaloids from Galipea officinalis trunk bark were studied. Crude extracts and pure alkaloids were tested for in vitro antimalarial activity on Plasmodium falciparum. The IC50 were evaluated after 24 and 72 h contact between compounds and the parasite culture, and ranged from 1.8 to 40 microg/ml for the chloroquine-sensitive strain (CQS) and from 0.09 to 38 microg/ml for the chloroquine-resistant strains (CQR). Galipinine yielded the best antimalarial effect (IC50: 0.09 - 0.9 microg/ml on CQR strain) and this compound interacted particularly between the 32(nd) and the 40(th) hour of the P. falciparum erythrocytic cycle. The cytotoxicity of the extracts and pure tetrahydroquinoline alkaloids was assessed on the HeLa cell line and showed IC50 values ranging from 5.8 to above 50 microg/ml.

14759742
Jenett-Siems K, Kohler I, Kraft C, Pertz HH, Kren V, Fiserova A, Kuzma M, Ulrichova J, Bienzle U, Eich E
In vitro antiplasmodial activities of semisynthetic N,N'-spacer-linked oligomeric ergolines.
Bioorg Med Chem. 2004 Feb 15;12(4):817-24.
Starting from three monomeric ergolines (terguride 1, festuclavine 2, pergolide 3) N,N'-spacer-linked oligomeric derivatives were prepared using different aliphatic or arylalkyl spacers. The compounds have been evaluated for their in vitro antiplasmodial activity against the chloroquine-sensitive strain poW and the chloroquine-resistant clone Dd2 of Plasmodium falciparum. Additionally, the cytotoxic effects against mouse fibroblasts (NIH 3T3) in vitro, and human hepatocytes were evaluated. All monomers displayed only a weak antiplasmodial effect, but N-1,N-1'-spacer-linked dimerization substantially enhanced their antiplasmodial activity. The best activities were observed for compounds showing a distance of six carbon atoms between two monomers, which can be obtained by aliphatic or p-xylene linkers. The N-6,N-6'-spacer-linked depropylpergolide dimer 3i exhibited the highest antiplasmodial activity of all compounds tested (IC(50) values: 0.14 and 0.13 microM against poW and Dd2, respectively). Unfortunately, it displayed toxic effects against the mouse fibroblast cell line NIH 3T3 (IC(50): 0.1+/-0.09 microM) and also against human hepatocytes at 100 microM (LDH-leakage: 15.58+/-0.87 microkat/L; GSH-level: 8.15+/-0.78 nmol/10(6) cells). However, the N-1,N-1'-spacer-linked trimer of festuclavine (2f), and also the N-1,N-1'-spacer-linked tetramer of terguride (1g) possessed remarkable antiplasmodial activities (IC(50): 0.54 and 1.53 microM, respectively, against Dd2) lacking cytotoxicity.

13679104
Jenett-Siems K, Kohler I, Kraft C, Siems K, Solis PN, Gupta MP, Bienzle U
Cornutins C-L, neo-clerodane-type diterpenoids from Cornutia grandifolia var. intermedia.
Phytochemistry. 2003 Oct;64(3):797-804.
Ten novel neo-clerodane diterpenoids, named cornutins C-L, have been isolated from the leaves of Cornutia grandifolia var. intermedia. Their structures have been elucidated by detailed spectroscopic analysis. In addition, the in vitro antiplasmodial activity of four isolated compounds (cornutin C-F) has been evaluated, revealing only a marginal activity.

12770583
Jenett-Siems K, Kraft C, Siems K, Jakupovic J, Solis PN, Gupta MP, Bienzle U
Sipaucins A-C, sesquiterpenoids from Siparuna pauciflora.
Phytochemistry. 2003 Jun;63(4):377-81.
The phytochemical investigation of the leaves of Siparuna pauciflora yielded three novel sesquiterpenoids: the germacrane sipaucin A, the elemane sipaucin B and sipaucin C, comprising a new type of carbon skeleton. In addition, four known aporphine alkaloids-nor-boldine, boldine, laurotetanine, and N-methyl-

laurotetanine-were obtained. The evaluation of the antiplasmodial activity of the isolated compounds against two strains of Plasmodium falciparum (PoW, Dd2) showed a moderate activity of nor-boldine.

10540301
Jenett-Siems K, Mockenhaupt FP, Bienzle U, Gupta MP, Eich E
In vitro antiplasmodial activity of Central American medicinal plants.
Trop Med Int Health. 1999 Sep;4(9):611-5.
The in vitro antiplasmodial activities of 14 plant species traditionally used in Central America for the treatment of malaria or fever were evaluated. Lipophilic extracts of Piper hispidum, Siparuna andina, S. pauciflora, S. tonduziana, and Xylopia cf. frutescens, proved to be active against both a chloroquine-sensitive and a resistant strain of Plasmodium falciparum. IC50 values ranged between 3.0 microg/ml and 21.9 microg/ml; however, moderate cytotoxicity of active extracts was observed. Bioactivity-guided fractionation of Piper hispidum yielded 2',4, 6'-trihydroxy-4'-methoxydihydrochalcone (asebogenin) as an active compound.

10865465
Jenett-Siems K, Siems K, Jakupovic J, Solis PN, Gupta MP, Mockenhaupt FP, Bienzle U, Eich E
Sipandinolide: a butenolide including a novel type of carbon skeleton from Siparuna andina.
Planta Med. 2000 May;66(4):384-5.
From a lipophilic extract of leaves of Siparuna andina (Monimiaceae), which exhibited antiplasmodial activity in vitro, two new compounds have been isolated: sipandinolide (1), a compound with a novel type of carbon skeleton and (-)-cis-3-acetoxy-4',5,7-trihydroxyflavanone (2). Their structures were established by spectroscopic methods; 2 showed moderate antiplasmodial activity whereas 1 was inactive.

12502338
Jensen JF, Kvist LP, Christensen SB
An antiplasmodial lignan from Euterpe precatoria.
J Nat Prod. 2002 Dec;65(12):1915-7.
As a part of a study on new antiplasmodial natural products, a new 8-5' linked lignan dehydrodiconiferyl dibenzoate (2) and p-hydroxybenzoic acid (1) were isolated from the roots of the palm Euterpe precatoria. In contrast to compound 1, compound 2 showed a moderate antiplasmodial activity.

12139461
Jonckers TH, van Miert S, Cimanga K, Bailly C, Colson P, De Pauw-Gillet MC, van den Heuvel H, Claeys M, Lemiere F, Esmans EL, Rozenski J, Quirijnen L, Maes L, Dommisse R, Lemiere GL, Vlietinck A, Pieters L
Synthesis, cytotoxicity, and antiplasmodial and antitrypanosomal activity of new neocryptolepine derivatives.
J Med Chem. 2002 Aug 1;45(16):3497-508.
On the basis of the original lead neocryptolepine or 5-methyl-5H-indolo[2,3-b]quinoline, an alkaloid from Cryptolepis sanguinolenta, derivatives were prepared using a biradical cyclization methodology. Starting from easily accessible educts, this approach allowed the synthesis of hitherto unknown compounds with a varied substitution pattern. As a result of steric hindrance, preferential formation of the 3-substituted isomers over the 1-substituted isomers was observed when cyclizing N-(3-substituted-phenyl)-N'-[2-(2-trimethylsilylethynyl)phenyl]carbodiimid es. All compounds were evaluated for their activity against chloroquine-sensitive as well as chloroquine-resistant Plasmodium falciparum strains, for their activity against Trypanosoma brucei and T. cruzi, and for their cytotoxicity on human MRC-5 cells. Mechanisms of action were investigated by testing heme complexation using ESI-MS, inhibition of beta-hematin formation, DNA interactions (DNA-methyl green assay and linear dichroism), and inhibition of human topoisomerase II. Neocryptolepine derivatives with a higher antiplasmodial activity and a lower cytotoxicity than the original lead have been obtained. This selective antiplasmodial activity was associated with inhibition of beta-hematin formation. 2-Bromoneocryptolepine was the most selective compound with an IC(50) value against chloroquine-resistant P. falciparum of 4.0 microM in the absence of cytotoxicity (IC(50) > 32 microM). Although cryptolepine, a known lead for antimalarials also originally isolated from Cryptolepis sanguinolenta, was more active (IC(50) = 2.0 microM), 2-bromoneocryptolepine showed a low affinity for DNA and no inhibition of human topoisomerase II, in contrast to cryptolepine. Although some neocryptolepine derivatives showed a higher antiplasmodial activity than 2-bromocryptolepine, these compounds also showed a higher affinity for DNA and/or a more pronounced cytotoxicity. Therefore, 2-bromoneocryptolepine is considered as the most promising lead from the present work for new antimalarial agents. In addition, 2-bromo-, 2-nitro-, and 2-methoxy-9-cyanoneocryptolepine exhibited antitrypanosomal activity in the micromolar range in the absence of obvious cytotoxicity.

16168652
Jullian V, Bonduelle C, Valentin A, Acebey L, Duigou AG, Prevost MF, Sauvain M

New clerodane diterpenoids from Laetia procera (Poepp.) Eichler (Flacourtiaceae), with antiplasmodial and antileishmanial activities.
Bioorg Med Chem Lett. 2005 Nov 15;15(22):5065-70.
Extracts of Laetia procera (Flacourtiaceae) displayed significant in vitro activity against Plasmodium falciparum. P. falciparum bioassay guided fractionation of a trunk bark extract of this plant led to the isolation of six clerodane diterpenoids (1-6) and a butanolide (7). Five of these compounds are new and called Laetiaprocerine A-D (3-6) and Laetianolide A (7). Their structures were established on the basis of 1D and 2D NMR experiments. Absolute configurations of 1 and 2 were determined by a modified Mosher's method and the absolute configuration of 5 by chemical correlation. The clerodane diterpenoids displayed activities against P. falciparum with an IC50 down to 0.5 microM on FCb1 and F32 strains, and also cytotoxicity toward human tumor cell line MCF7. The most active compound showed a selectivity index of 6.8. Some of these compounds also displayed activities against Leishmania amazonensis amastigote axenic stages and promastigote.

16504432
Jullian V, Bourdy G, Georges S, Maurel S, Sauvain M
Validation of use of a traditional antimalarial remedy from French Guiana, Zanthoxylum rhoifolium Lam.
J Ethnopharmacol. 2006 Feb 25;.
Zanthoxylum rhoifolium bark (Rutaceae) is a medicinal plant, traditionally used in French Guiana to treat and prevent malaria. Bioassay-guided extractions of Zanthoxylum rhoifolium bark have shown that antiplasmodial activity is concentrated in the alkaloid fraction. Further fractionation of this extract has yielded seven benzophenanthridine alkaloids, dihydroavicine 1, dihydronitidine 2, oxyavicine 3, oxynitidine 4, fagaridine 5, avicine 6 and nitidine 7. Antimalarial activity of the last five compounds has been evaluated, and nitidine was the most potent, displaying an IC(50)

15013184
Kamanzi Atindehou K, Schmid C, Brun R, Kone MW, Traore D
Antitrypanosomal and antiplasmodial activity of medicinal plants from Cote d'Ivoire.
J Ethnopharmacol. 2004 Feb;90(2-3):221-7.
The antitrypanosomal activity of 101 crude ethanol extracts derived from 88 medicinal plants from Cote d'Ivoire was determined in vitro using Trypanosoma brucei rhodesiense. Of those extracts 8 showed good activity (IC50 values < or =8 microg/ml), 37 revealed a weak activity (IC50 values between 25 and 8.1 microg/ml) and 56 did not show any activity at all (IC50 values >25 microg/ml). The extracts of Enantia polycarpa (Annonaceae) and Trichilia emetica (Meliaceae) were the most promising ones. Their IC50 values were 0.5 and 0.04 microg/ml, respectively, and the selectivity index 616 and 209, respectively. This is the first report of in vitro antitrypanosomal activity of these two plants. Their high activities render them candidates for the isolation of compounds which could develop into new lead structures for drug development programs against African trypanosomiasis. Seven of the tested extracts exhibited an antiplasmodial activity against K1 strain of Plasmodium falciparum with IC50 values below 4 microg/ml. The highest activity was found for Enantia polycarpa stem bark with an IC50 value of 0.126 microg/ml.

15885942
Kanokmedhakul K, Kanokmedhakul S, Phatchana R
Biological activity of Anthraquinones and Triterpenoids from Prismatomeris fragrans.
J Ethnopharmacol. 2005 Sep 14;100(3):284-8.
A new 1,3-dihydroxy-2-methyl-5,6-dimethoxyanthraquinone (1); six known anthraquinones, nordamnacanthal (2), damnacanthal (3), rubiadin (4), rubiadin-1-methyl ether (5), lucidin-omega-methyl ether (6), and 1-hydroxy-2-hydroxymethyl-3-methoxyanthraquinone (7); a beta-sitosterol (8); together with two known triterpenoids, beta-acetylolean-12-en-28-olic acid (9), and 3beta-O-acetyl-11alpha,12alpha-epoxyolean-28,13-olide (10) were isolated from the roots and stems of Prismatomeris fragrans. Their structures were established on the basis of spectral data. This is the first isolation of compounds 2, 6, 7, 9 and 10 from Prismatomeris genus. The isolated compounds were evaluated in antiplasmodial, antituberculosis, antifungal and anticancer cell lines tests. The bioactivity assays showed that only 9 exhibited moderate antimalarial activity, 2 and 3 exhibited antifungal activity while 2, 3, 4, 7 and 9 showed antituberculosis activity. In addition, compounds 2, 3 and 7 exhibited cytotoxicity to BC cell line while 1, 1a (the methyl ether derivative of 1), 2, 3, 4, 5, and 9 exhibited cytotoxicity to NCI-H187 cell line.

16441071
Kanokmedhakul S, Kanokmedhakul K, Kantikeaw I, Phonkerd N
2-substituted furans from the roots of Polyalthia evecta.
J Nat Prod. 2006 Jan;69(1):68-72.
Four new 2-substituted furans, 19-(2-furyl)nonadeca-5,7-diynoic acid (1), 19-(2-furyl)nonadeca-5-ynoic acid (2), 1-(2-furyl)pentacosa-7,9-diyne (3), and ester 21-(2-furyl)heneicosa-14,16-diyne-19-(2-furyl)nonadeca-

5,7-diynoate (4) have been isolated from the roots of Polyalthia evecta. Their structures were established by spectroscopic techniques. Compounds 1 and 1a showed antiplasmodial activity. The acids 1 and 2 exhibited antiviral activity against Herpes simplex type 1. In addition, 5 also showed cytotoxicity against the NCI-H187 cell line.

12139464
Kaschula CH, Egan TJ, Hunter R, Basilico N, Parapini S, Taramelli D, Pasini E, Monti D
Structure-activity relationships in 4-aminoquinoline antiplasmodials. The role of the group at the 7-position.
J Med Chem. 2002 Aug 1;45(16):3531-9.
Antiplasmodial activities versus the chloroquine sensitive D10 strain of Plasmodium falciparum of a series of N(1),N(1)-diethyl-N(2)-(4-quinolinyl)-1,2-ethanediamines with 11 different substituents at the 7-position on the quinoline ring have been investigated in vitro. Electron-withdrawing groups at the 7-position have been shown to lower the pK(a) of both the quinoline ring nitrogen atom and the tertiary amino nitrogen in the alkyl side chain. The quinoline nitrogen pK(a) ranges from 6.28 in the nitro derivative to 8.36 in the amino derivative, while the tertiary amino nitrogen has a pK(a) ranging between 7.65 in the trifluoromethyl derivative and 10.02 in the amino derivative. Calculation suggests that the resulting pH trapping of these compounds in the parasite food vacuole ranges between about 7% of that observed in chloroquine for the NO(2) derivative and 97% in the amino derivative. A direct proportionality between antiplasmodial activity normalized for pH trapping and beta-hematin inhibitory activity was observed. Activity could not be correlated with any other observed physical parameter. The beta-hematin inhibitory activity of these derivatives appears to correlate with both the hematin-quinoline association constant and the electron-withdrawing capacity of the group at the 7-position (Hammett constant). For the compounds under investigation, the hematin association constant is in turn influenced by the lipophilicity of the group at the 7-position.

11731912
Kayser O, Kiderlen AF, Brun R
In vitro activity of aurones against Plasmodium falciparum strains K1 and NF54.
Planta Med. 2001 Nov;67(8):718-21.
A series of naturally occurring aurones (e. g., Rubiaceae, Cyperaceae) was synthesized and tested for the ability to inhibit erythrocytic stages of Plasmodium falciparum strains in vitro. Some of the these compounds exhibited antiplasmodial activity in the micromol range, determined as fifty percent-inhibitory concentrations (IC(50)). Drug activity was not associated with cytotoxicity for the mammalian tumor cell lines KB and SKMel (IC(50) > 3.0 microM). The most active compound was 4,6,4'-triacetyl-3',5'-dimethoxy-2-aurone with IC(50) values of 0.007 microM and 0.18 microM for the P. falciparum strains K1 and NF54, respectively. Interestingly, the multiple drug-resistant P. falciparum strain K1 was more sensitive to tested aurones than the drug-susceptible strain NF54.

10630106
Keawpradub N, Kirby GC, Steele JC, Houghton PJ
Antiplasmodial activity of extracts and alkaloids of three Alstonia species from Thailand.
Planta Med. 1999 Dec;65(8):690-4.
Methanol extracts prepared from various parts of Alstonia scholaris, A. macrophylla and A. glaucescens, collected from Thailand, have been assessed for antiplasmodial activity against multidrug-resistant K1 strain of Plasmodium falciparum cultured in human erythrocytes. Pronounced antiplasmodial activity was exhibited by methanol extract of the root bark of A. macrophylla with an IC50 value of 5.7 micrograms/ml. Thirteen indole alkaloids were isolated from the active extract. These alkaloids and a semisynthetic bisindole O-acetylmacralstonine were subsequently tested against the K1 strain of P. falciparum. Pronounced antiplasmodial activity was observed mainly among the bisindole alkaloids, particularly villalstonine and macrocarpamine with IC50 values of 0.27 and 0.36 microM, respectively. The potent alkaloids were further tested against T9-96, the chloroquine-sensitive strain of P. falciparum. It has been found that the active alkaloids, in contrast to chloroquine, have significantly higher affinity to the K1 strain than to the T9-96 strain.

16321410
Kenmogne M, Prost E, Harakat D, Jacquier MJ, Frederich M, Sondengam LB, Zeches M, Waffo-Teguo P
Five labdane diterpenoids from the seeds of Aframomum zambesiacum.
Phytochemistry. 2006 Mar;67(5):433-8.
Five labdane diterpenoids, (3-5), zambesiacolactone A (7) and zambesiacolactone B (8), were isolated from the seeds of Aframomum zambesiacum (Baker) K. Schum., along with five known labdanes and a linear sesquiterpene, nerolidol. Their structures were elucidated by spectroscopic analysis. Their antiplasmodial activity was evaluated in vitro against Plasmodium falciparum. Compound 3 was the most active with an IC(50) value of 4.97muM.

10869210
Kirsch G, Kong GM, Wright AD, Kaminsky R
A new bioactive sesterterpene and antiplasmodial alkaloids from the marine sponge hyrtios cf. erecta.
J Nat Prod. 2000 Jun;63(6):825-9.
From the CH(2)Cl(2) extract of the sponge Hyrtios cf. erecta, collected from Fiji, two new sesterterpenes, 1 and 2, and the known compounds isodehydroluffariellolide (3), homofascaplysin A (4), and fascaplysin (5) were isolated. The structures of 1-5 were established employing 1D and 2D NMR spectroscopy and mass spectrometry. All NMR resonances of fascaplysin (5) have been unambiguously assigned. Evaluation of the biological activity of the extracts and pure compounds toward Plasmodium falciparum, Trypanosoma brucei subsp. rhodesiense, Trypanosoma cruzi, hepatitis A virus (HAV), several other microbial targets, and HIV-1-RT and p56(lck) tyrosine kinase revealed new activities for homofascaplysin (4) and fascaplysin (5), both being potently active in vitro against P. falciparum.

12837742
Klenke B, Barrett MP, Brun R, Gilbert IH
Antiplasmodial activity of a series of 1,3,5-triazine-substituted polyamines.
J Antimicrob Chemother. 2003 Aug;52(2):290-3. Epub 2003 Jul 1.
Polyamine biosynthesis and function has been shown to be a good drug target in some parasitic protozoa and it is proposed that the pathway might also represent a target in the malaria parasite Plasmodium falciparum. A series of 1,3,5-triazine-substituted polyamine analogues were tested for activity against Plasmodium falciparum in vitro. The series showed activity against the parasites and were generally more active against the chloroquine-resistant line K1 than the chloroquine-susceptible line NF54. Simple unbranched analogues had better activity than analogues carrying branched or cyclic central chains. Addition of multiple triazine units in general led to increased activity of the compounds.

14659482
Kluza J, Baldeyrou B, Colson P, Rasoanaivo P, Mambu L, Frappier F, Bailly C
Cytotoxicity and DNA binding properties of the plant alkaloid burasaine.
Eur J Pharm Sci. 2003 Dec;20(4-5):383-91.
Burasaine is a plant alkaloid isolated from the roots of several species of the Burasaia genus endemic to Madagascar. It exhibits in vitro antiplasmodial activities but the molecular basis of this biological activity is not known. The strong structural similarity with the alkaloid berberine prompted us to postulate that burasaine could interact with DNA. To test this hypothesis, we investigated the mode of binding of burasaine to DNA and tested its cytotoxic potential toward human HL-60 leukemia cells. Its inhibitory activity toward topoisomerases I and II was also studied. Absorption and melting temperature measurements attested that burasaine forms stable complexes with DNA. The results of electric linear dichroism (ELD) spectroscopy may be interpreted either by an intercalation or by an external stacking parallel to the base pairs. The affinity of burasaine for DNA is slightly lower than that of berberine and this translates at the cellular level by a reduced cytotoxicity. Burasaine does not promote DNA cleavage by human topoisomerases I or II and this likely accounts for its very weak cytotoxic potential and its very modest effects on the cell cycle progression observed at high concentrations. The study identifies DNA as a potential bioreceptor for burasaine and contributes to a better understanding of the mechanism of action of benzoquinolizine alkaloids.

15878245
Koch A, Tamez P, Pezzuto J, Soejarto D
Evaluation of plants used for antimalarial treatment by the Maasai of Kenya.
J Ethnopharmacol. 2005 Oct 3;101(1-3):95-9.
Semi-structured interviews with three Maasai herbalists led to the identification and collection of 21 species of plants used to treat malaria. Extracts were evaluated using in vitro antimalarial and cytotoxicity assays. Of the species tested, over half were antiplasmodial (IC5020 microg/ml) against cultured KB cells. The results of this preliminary investigation support the traditional knowledge of Maasai herbalists and justify ethnomedical inquiry as a promising method, specifically, in antimalarial therapy, to yield leads for drug discovery.

11270733
Kohler I, Jenett-Siems K, Mockenhaupt FP, Siems K, Jakupovic J, Gonzalez JC, Hernandez MA, Ibarra RA, Berendsohn WG, Bienzle U, Eich E
In vitro antiplasmodial activity of 4-phenylcoumarins from Exostema mexicanum.
Planta Med. 2001 Feb;67(1):89-91.
The stem bark of Exostema mexicanum (Rubiaceae) is used in Latin American folk medicine as a quinine substitute for malaria treatment. Bioassay-guided fractionation of lipophilic and hydrophilic extracts from the stem bark and branches yielded two previously undescribed 4-phenylcoumarins: 4',8-dihydroxy-5,7-dimethoxy-4-phenylcoumarin (exomexin A) and 3',4'-dihydroxy-5,7,8-trimethoxy-4-phenylcoumarin (exomexin B). Together with five known derivatives the in vitro activities against a chloroquine-sensitive

strain (poW) and a chloroquine-resistant strain (Dd2) of Plasmodium falciparum have been evaluated. The most lipophilic compound, 4',5,7,8-tetramethoxy-4-phenylcoumarin (O-methylexostemin) revealed the strongest antiplasmodial activity (IC50 values: 3.6 microg/ml [poW], 1.6 microg/ml [Dd2]).

12064726
Kohler I, Jenett-Siems K, Siems K, Hernandez MA, Ibarra RA, Berendsohn WG, Bienzle U, Eich E
In vitro antiplasmodial investigation of medicinal plants from El Salvador.
Z Naturforsch [C]. 2002 Mar-Apr;57(3-4):277-81.
In vitro antiplasmodial activities of extracts from Albizia saman, Fabaceae, Calea tenuifolia (C. zacatechichi), Asteraceae, Hymenaea courbaril, Fabaceae, Jatropha curcas, Euphorbiaceae, Momordica charantia, Cucurbitaceae, and Moringa oleifera, Moringaceae were evaluated. From the lipophilic extract of C tenuifolia five active flavones were obtained. 4',5-Dihydroxy-7-methoxyflavone [genkwanin] and 5-hydroxy-4',7-dimethoxyflavone [apigenin 4',7-dimethylether] exhibited the strongest antiplasmodial activity against a chloroquine-sensitive strain (poW) and a chloroquine-resistant strain (Dd2) of Plasmodium falciparum [IC50 values: 17.1-28.5 microM). Furthermore octadeca-9,12-dienoic acid [linoleic acid] [IC50] values of 21.8 microM (poW) and 31.1 microM (Dd2)] and octadeca-9,12,15-trienoic acid (alpha-linolenic acid) were isolated.

12009320
Kraft C, Jenett-Siems K, Kohler I, Tofern-Reblin B, Siems K, Bienzle U, Eich E
Antiplasmodial activity of sesquilignans and sesquineolignans from Bonamia spectabilis.
Phytochemistry. 2002 May;60(2):167-73.
Phytochemical re-investigation of the aerial parts of Bonamia spectabilis (Convolvulaceae) led to the isolation of four minor tetrahydrofuran-type sesquilignans (bonaspectins E-H) together with the known neolignan virolongin A and the known lignan rel-(7S,8R,7'R,8'R)-3,3',4,4',5,5'-hexamethoxylignan. Their structures were established on the basis of spectral data. These six compounds as well as further seven lignanoids from B. spectabilis, characterised previously, were tested for their antiplasmodial activity against a chloroquine-sensitive strain (PoW) and a chloroquine-resistant clone (Dd2) of Plasmodium falciparum. Bonaspectin C 4"-O-glucoside, its aglycone, and bonaspectin D 4"-O-glucoside revealed the highest antiplasmodial activities (IC50 values: 1.3, 2.0, 6.5 microM [PoW]; 1.7, 4.6, 3.7 microM [Dd2], respectively).

11025148
Kraft C, Jenett-Siems K, Siems K, Gupta MP, Bienzle U, Eich E
Antiplasmodial activity of isoflavones from Andira inermis.
J Ethnopharmacol. 2000 Nov;73(1-2):131-5.
The stem bark and seeds of Andira inermis, Fabaceae, are employed as a purgative, vermifuge, and febrifuge. In particular, the powdered bark is claimed to be efficacious in intermittent fever. Bioassay-guided fractionation of lipophilic extracts from the stems and leaves yielded six isoflavones: biochanin A, calycosin, formononetin, genistein, pratensein, and prunetin. Calycosin (3', 7-dihydroxy-4'-methoxyisoflavone) and genistein (4',5, 7-trihydroxyisoflavone) have been shown to possess in vitro activity against the chloroquine-sensitive strain poW and the chloroquine-resistant clone Dd2 of Plasmodium falciparum.

12601673
Kraft C, Jenett-Siems K, Siems K, Jakupovic J, Mavi S, Bienzle U, Eich E
In vitro antiplasmodial evaluation of medicinal plants from Zimbabwe.
Phytother Res. 2003 Feb;17(2):123-8.
In this study the in vitro antiplasmodial activities of extracts from Cussonia spicata (Araliaceae), Artemisia afra, Vernonia colorata, V. natalensis (Asteraceae), Parinari curatellifolia (Chrysobalanaceae), Clutia hirsuta, Flueggea virosa, (Euphorbiaceae), Adenia gummifera (Passifloraceae) and Hymenodictyon floribundum, (Rubiaceae) were evaluated. The lipophilic extracts from the aerial parts of Artemisia afra and Vernonia colorata proved to be the most active against the chloroquine-sensitive strain PoW and against the chloroquine-resistant clone Dd2 of Plasmodium falciparum. Bioassay-guided fractionation of the extract of A. afra yielded seven flavonoids, from which acacetin, genkwanin and 7-methoxyacacetin showed in vitro activity; the IC(50) values ranged from 4.3 microgram/mL to 12.6 microgram/mL. In addition, several sesquiterpene lactones could be obtained from the most active fractions. Whereas eudesmaafraglaucolide proved to be inactive, the guaianolides 1-desoxy-1alpha-peroxy-rupicolin A-8-O-acetate, 1alpha,4alpha-dihydroxybishopsolicepolide and rupicolin A-8-O-acetate revealed in vitro antiplasmodial activity. Evaluation of V. colorata gained four sesquiterpenes 11beta,13-dihydrovernodalin, vernodalol, 11beta,13-dihydrovernolide and 11beta,13,17,18-tetrahydrovernolide, from which the first two constituents exhibited the strongest antiplasmodial activity (IC(50) values: 1.1-4.8 microgram/mL).

11672743
Kraft C, Jenett-Siems K, Siems K, Solis PN, Gupta MP, Bienzle U, Eich E

Andinermals A-C, antiplasmodial constituents from Andira inermis.
Phytochemistry. 2001 Nov;58(5):769-74.
Bioassay-guided fractionation of the leaves from Andira inermis was undertaken as part of a screening program to verify the traditional use of herbal remedies against malaria. Among the isolated phenolic compounds three novel 2-arylbenzofuran-3-carbaldehydes, andinermal A-C, were obtained together with a new flavanonol glycoside, taxifolin-3-O-(3"-O-trans-cinnamoyl)-alpha-L-rhamnopyranoside.

12027771
Kuria KA, Chepkwony H, Govaerts C, Roets E, Busson R, De Witte P, Zupko I, Hoornaert G, Quirynen L, Maes L, Janssens L, Hoogmartens J, Laekeman G
The antiplasmodial activity of isolates from Ajuga remota.
J Nat Prod. 2002 May;65(5):789-93.
Ajuga remota is the most frequently used medicinal herb for malaria treatment in Kenya. Its two known isolates ajugarin-1 (1) and ergosterol-5,8-endoperoxide (3) and a new isolate 8-O-acetylharpagide (2) were evaluated for their in vitro antiplasmodial activity. Ajugarin-1 was moderately active, with an IC(50) of 23.0 +/- 3.0 microM, as compared to chloroquine (IC(50) = 0.041 +/- 0.003 microM) against the chloroquine-sensitive (FCA 20/GHA) strain of Plasmodium falciparum. Ergosterol-5,8-endoperoxide was about 3x as potent (IC(50) = 8.2 +/- 1.1 microM), while 8-O-acetylharpagide, whose structure was established by spectroscopic evidence, was inactive. Both ajugarin-1 and ergosterol-5,8-endoperoxide did not exhibit cytotoxicity against A431 (skin carcinoma) cell line, but 8-O-acetylharpagide was significantly cytotoxic. This iridoid glucoside, which has been formerly isolated from Ajuga decumbens, was identified in A. remota for the first time.

15588325
Labaied M, Dagan A, Dellinger M, Geze M, Egee S, Thomas SL, Wang C, Gatt S, Grellier P
Anti-Plasmodium activity of ceramide analogs.
Malar J. 2004 Dec 10;3(1):49.
BACKGROUND: Sphingolipids are key molecules regulating many essential functions in eukaryotic cells and ceramide plays a central role in sphingolipid metabolism. A sphingolipid metabolism occurs in the intraerythrocytic stages of Plasmodium falciparum and is associated with essential biological processes. It constitutes an attractive and potential target for the development of new antimalarial drugs. METHODS: The anti-Plasmodium activity of a series of ceramide analogs containing different linkages (amide, methylene or thiourea linkages) between the fatty acid part of ceramide and the sphingoid core was investigated in culture and compared to the sphingolipid analog PPMP (d,1-threo-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol). This analog is known to inhibit the parasite sphingomyelin synthase activity and block parasite development by preventing the formation of the tubovesicular network that extends from the parasitophorous vacuole to the red cell membrane and delivers essential extracellular nutrients to the parasite. RESULTS: Analogs containing methylene linkage showed a considerably higher anti-Plasmodium activity (IC50 in the low nanomolar range) than PPMP and their counterparts with a natural amide linkage (IC50 in the micromolar range). The methylene analogs blocked irreversibly P. falciparum development leading to parasite eradication in contrast to PPMP whose effect is cytostatic. A high sensitivity of action towards the parasite was observed when compared to their effect on the human MRC-5 cell growth. The toxicity towards parasites did not correlate with the inhibition by methylene analogs of the parasite sphingomyelin synthase activity and the tubovesicular network formation, indicating that this enzyme is not their primary target. CONCLUSIONS: It has been shown that ceramide analogs were potent inhibitors of P. falciparum growth in culture. Interestingly, the nature of the linkage between the fatty acid part and the sphingoid core considerably influences the antiplasmodial activity and the selectivity of analogs when compared to their cytotoxicity on mammalian cells. By comparison with their inhibitory effect on cancer cell growth, the ceramide analogs might inhibit P. falciparum growth through modulation of the endogenous ceramide level.

12064727
Lang G, Passreiter CM, Wright CW, Filipowicz NH, Addae-Kyereme J, Medinilla BE, Castillo JJ
Antiplasmodial activities of sesquiterpene lactones from Eupatorium semialatum.
Z Naturforsch [C]. 2002 Mar-Apr;57(3-4):282-6.
Eupatorium semialatum, Plasmodium falciparum, Sesquiterpene Lactones Eupatorium semialatum is a member of the Asteraceae, which occurs in Guatemala. Previously, we reported the occurrence of sesquiterpene lactones of the eudesmanolide type as main constituents in the leaves. This paper deals with the isolation and identification of the first guaianolide found in E. semialatum. Since this plant is used against malaria and other diseases in the Guatemalan folk medicine, the main sesquiterpene lactones were tested for their activities against Plasmodium falciparum in vitro.

14640524
Lang'at-Thoruwa C, Kirby GC, Phillipson JD, Warhurst DC, Watt RA, Wright CW
Enhancement of the antiplasmodial activity of quassin by transformation into a gamma-lactone.

J Nat Prod. 2003 Nov;66(11):1486-9.
The naturally occurring bitter principle quassin (1) was converted chemically into the gamma-lactone quassilactone (13) in an attempt to enhance its antiplasmodial activity. The in vitro antiplasmodial activity of 13 against Plasmodium falciparum (K1) (IC(50) = 23 microM) was 40-fold greater than that of 1. However, one of the intermediates, compound 8, the 15beta-hydroxy,16-O-m-chlorobenzoyl analogue of 1, was 506-fold more active than 1 against P. falciparum (IC(50) = 1.8 microM) and only 3-fold less potent than chloroquine. In addition, 8 displayed the best cytotoxic/antiplasmodial ratio (112) of all of the compounds tested. In the course of this work a dimer, neoquassin ether (6), linked at C-16 was also prepared; 6 was found to have weak antiplasmodial activity (IC(50) = 9.7 microM).

12142990
Lansiaux A, Bailly C, Houssier C, Colson P, De Pauw-Gillet MC, Frederich M, Tits M, Angenot L
Apoptosis of HL-60 leukemia cells induced by the bisindole alkaloids sungucine and isosungucine from Strychnos icaja.
Planta Med. 2002 Jul;68(7):591-5.
Sungucine and isosungucine are two bisindole alkaloids isolated from the roots of the African plant Strychnos icaja Baillon. They both exhibit antiplasmodial activities but also show cytotoxic effects against human cancer cell lines. In order to elucidate their mechanism of action, we have investigated the interaction of the alkaloids with DNA and their capacity to inhibit nucleic acids and protein synthesis in the human HL-60 promyelocytic leukemia cell line. Cell treatment with both sungucine and isosungucine leads to the appearance of a hypo-diploid DNA content peak. Western blotting analysis reveals that the two alkaloids induce cleavage of the poly(ADP-ribose) polymerase (PARP) and promote the cleavage of a caspase-3 DEVD peptide substrate. The activation of the caspase cascade is accompanied with a fragmentation of DNA in cells, as revealed by the TUNEL assay. Altogether, the results shed light on the mechanism of action of these two plant alkaloids and identify signaling factors involved in (iso)sungucine-induced apoptosis in HL-60 cells.

16513357
Laurent D, Jullian V, Parenty A, Knibiehler M, Dorin D, Schmitt S, Lozach O, Lebouvier N, Frostin M, Alby F, Maurel S, Doerig C, Meijer L, Sauvain M
Antimalarial potential of xestoquinone, a protein kinase inhibitor isolated from a Vanuatu marine sponge Xestospongia sp.
Bioorg Med Chem. 2006 Feb 28;.
As part of our search for new antimalarial drugs, we have screened for inhibitors of Pfnek-1, a protein kinase of Plasmodium falciparum, in south Pacific marine sponges. On the basis of a preliminary screening, the ethanolic crude extract of a new species of Xestospongia collected in Vanuatu was selected for its promising activity. A bioassay-guided fractionation led us to isolate xestoquinone which inhibits Pfnek-1 with an IC(50) around 1muM. Among a small panel of plasmodial protein kinases, xestoquinone showed modest protein kinase inhibitory activity toward PfPK5 and no activity toward PfPK7 and PfGSK-3. Xestoquinone showed in vitro antiplasmodial activity against a FCB1 P. falciparum strain with an IC(50) of 3muM and a weak selectivity index (SI 7). Xestoquinone exhibited a weak in vivo activity at 5mg/kg in Plasmodium berghei NK65 infected mice and was toxic at higher doses.

15114511
Limmatvapirat C, Sirisopanaporn S, Kittakoop P
Antitubercular and antiplasmodial constituents of Abrus precatorius.
Planta Med. 2004 Mar;70(3):276-8.
A known isoflavanquinone, abruquinone B (1), and a new derivative, abruquinone G (2), were isolated from the aerial parts of Abrus precatorius. Chemical structures of these compounds were elucidated by spectral analyses. While 1 exhibited antitubercular, antiplasmodial and cytotoxic activities, compound 2 showed mild antiviral and cytotoxic activities.

15234773
Lohombo-Ekomba ML, Okusa PN, Penge O, Kabongo C, Choudhary MI, Kasende OE
Antibacterial, antifungal, antiplasmodial, and cytotoxic activities of Albertisia villosa.
J Ethnopharmacol. 2004 Aug;93(2-3):331-5.
Albertisia villosa (Menispermaceae) is a subtropical medicinal plant that is widely used in traditional African medicines against various diseases. Three known bisbenzylisoquinoline alkaloids; cycleanine, cocsoline, and N-desmethylcycleanine have been identified. Cycleanine, the most abundant (85%) of all identified bisbenzylisoquinoline alkaloids, accounts for all of the activity of the crude drug. The biological screening of cycleanine and the root bark alkaloidal extract revealed potent antibacterial, antifungal, antiplasmodial, and cytotoxic activities. These results may partly explain and support the use of Albertisia villosa root barks for the treatment of malaria and other infectious diseases in traditional Congolese medicine.

15280000
Loyola LA, Borquez J, Morales G, San-Martin A, Darias J, Flores N, Gimenez A
Mulinane-type diterpenoids from Azorella compacta display antiplasmodial activity.
Phytochemistry. 2004 Jul;65(13):1931-5.
Two mulinane-type diterpenoids were isolated from Azorella compacta; namely 20-hydroxymulin-11,13-dienyl acetate and 13,14-dihydroxymulin-11-en-20-oic acid. The structures were elucidated by analysis of their spectroscopic data. These compounds, as well as three previously isolated diterpenes, were evaluated as potential in vivo growth inhibitors of Plasmodium berghei NK 65 on infected mice at an intraperitoneal dose of 10 mg/kg/day. Sixty percent and forty-two percent growth inhibition were obtained with 17-acetoxymulin-11,13-dien-20-oic acid and 13, 14-dihydroxymulin-11-en-20-oic acid, respectively.

10985080
Mambu L, Martin MT, Razafimahefa D, Ramanitrahasimbola D, Rasoanaivo P, Frappier F
Spectral characterisation and antiplasmodial activity of bisbenzylisoquinolines from Isolona ghesquiereina.
Planta Med. 2000 Aug;66(6):537-40.
From stem barks of Isolona guesquiereina three known bisbenzylisoquinolines were isolated and identified as (-)-curine, chondrofoline and isochondodendrine. Structures were established mainly on the basis of comparison of their physical and spectral data with published data for them and their methylated derivatives. Cleavage with sodium in liquid ammonia was necessary to unambiguously determine the stereochemistry of (-)-curine and subsequently establish its stereochemical link with chondrofoline, erroneously assigned as 7-O-methyl-(+)-curine. Complete and unambiguous 1H-, 15N- and 13C-NMR assignments of the three alkaloids were made by means of 2D-NMR techniques namely, COSY, HMQC, gs-HMQC, HMBC and NOESY. (-)-Curine, isochondrodendrine and their methylated derivatives were shown to exhibit strong in vitro antiplasmodial activity and in vivo activity was also observed for (-)-curine.

10411941
Mamoun CB, Gluzman IY, Goyard S, Beverley SM, Goldberg DE
A set of independent selectable markers for transfection of the human malaria parasite Plasmodium falciparum.
Proc Natl Acad Sci U S A. 1999 Jul 20;96(15):8716-20.
Genomic information is rapidly accumulating for the human malaria pathogen, Plasmodium falciparum. Our ability to perform genetic manipulations to understand Plasmodium gene function is limited. Dihydrofolate reductase is the only selectable marker presently available for transfection of P. falciparum. Additional markers are needed for complementation and for expression of mutated forms of essential genes. We tested parasite sensitivity to different drugs for which selectable markers are available. Two of these drugs that were very effective as antiplasmodial inhibitors in culture, blasticidin and geneticin (G418), were selected for further study. The genes BSD, encoding blasticidin S deaminase of Aspergillus terreus, and NEO, encoding neomycin phosphotransferase II from transposon Tn 5, were expressed under the histidine-rich protein III (HRPIII) gene promoter and tested for their ability to confer resistance to blasticidin or G418, respectively. After transfection, blasticidin and G418-resistant parasites tested positive for plasmid replication and BSD or NEO expression. Cross-resistance assays indicate that these markers are independent. The plasmid copy number and the enzymatic activity depended directly on the concentration of the drug used for selection. These markers set the stage for new methods of functional analysis of the P. falciparum genome.

15322625
Marcano TJ, Morgado A, Tosta CE, Coura JR
Cross-sectional study defines difference in malaria morbidity in two Yanomami communities on Amazonian boundary between Brazil and Venezuela.
Mem Inst Oswaldo Cruz. 2004 Jun;99(4):369-76. Epub 2004 Aug 13.
It is well established that immunity to malaria is short-lived and is maintained by the continuous contact with the parasite. We now show that the stable transmission of malaria in Yanomami Amerindian communities maintains a degree of immunity in the exposed population capable to reduce prevalence and morbidity of malaria. We examined 508 Yanomami Amerindians living along Orinoco (407) and Mucajai (101) rivers, on the Venezuelan and Brazilian Amazon region, respectively. At Orinoco villages, malaria was hyperendemic and presented stable transmission, while at Mucajai villages it was mesoendemic and showed unstable transmission. The frequency of Plasmodium vivax and P. falciparum was roughly comparable in Venezuelan and Brazilian communities. Malaria presented different profiles at Orinoco and Mucajai villages. In the former communities, malaria showed a lower prevalence (16% x 40.6%), particularly among those over 10 years old (5.2% x 34.8%), a higher frequency of asymptomatic cases (38.5% x 4.9%), and a lower frequency of cases of severe malaria (9.2% x 36.5%). Orinoco villagers also showed a higher reactivity of the immune system, measured by the frequency of splenomegaly (72.4% x 29.7%) and by the splenic index (71.4% over level 1 x 28.6), and higher prevalence (91.1% x 72.1%) and mean titer (1243 x 62) of antiplasmodial IgG antibodies,

as well as a higher prevalence (77.4% x 24.7%) and mean titer (120 x 35) of antiplasmodial IgM antibodies. Our findings show that in isolated Yanomami communities the stability of malaria transmission, and the consequent continuous activation of the immune system of the exposed population, leads to the reduction of malaria prevalence and morbidity.

10925402
Marshall SJ, Russell PF, Phillipson JD, Kirby GC, Warhurst DC, Wright CW
Antiplasmodial and antiamoebic activities of medicinal plants from Sierra Leone.
Phytother Res. 2000 Aug;14(5):356-8.
Crude ethanol extracts of 18 medicinal plants from Sierra Leone, West Africa were examined for antiplasmodial activity against Plasmodium falciparum, using an in vitro microtest. Eleven of these extracts were also screened for in vitro antiamoebic activity against Entamoeba histolytica. Only one plant extract, Triclisia patens (Menispermaceae) showed significant antiplasmodial activity (IC(50) = 8 microg/mL). None of the plant extracts was effective against Entamoeba histolytica.

15115412
Mayence A, Vanden Eynde JJ, Krogstad FM, Krogstad DJ, Cushion MT, Huang TL
Parallel solution-phase synthesis of conformationally restricted congeners of pentamidine and evaluation of their antiplasmodial activities.
J Med Chem. 2004 May 6;47(10):2700-5.
Conformationally restricted bisbenzamidines and related congeners have been synthesized and evaluated for activity against two Plasmodium falciparum strains. The most active compounds, bisbenzamidines linked by a 1,4-piperazinediyl core, had IC(50) values between 3 and 18 nM against both chloroquine-susceptible and -resistant parasites and IC(50) values for cytotoxicity greater than 5 microM, using the A549 human lung epithelial cell line. DNA binding affinity, as estimated by DeltaT(m), did not correlate with either antiparasite effects or cytotoxicity. Each of the active bisbenzamidines interfered with the formation of hemozoin in cell-free systems.

16257160
Mbatchi SF, Mbatchi B, Banzouzi JT, Bansimba T, Nsonde Ntandou GF, Ouamba JM, Berry A, Benoit-Vical F
In vitro antiplasmodial activity of 18 plants used in Congo Brazzaville traditional medicine.
J Ethnopharmacol. 2006 Mar 8;104(1-2):168-174. Epub 2005 Oct 27.
Sixty-six extracts of 18 plants commonly used by traditional healers in Congo Brazzaville for the treatment of malaria have been investigated for in vitro antiplasmodial activity. Ethanolic and dichloromethane extracts of 7 among the 18 studied plants were moderately active (10mug/ml<IC(50)

16233959
Medjroubi K, Benayache F, Bermejo J
Sesquiterpene lactones from Centaurea musimomum. Antiplasmodial and cytotoxic activities.
Fitoterapia. 2005 Dec;76(7-8):744-6. Epub 2005 Oct 17.
The chloroform extract of the aerial parts of Centaurea musimomum exhibited significant activity against Plasmodium falciparum. The phytochemical study of this extract gave seven native and four acetylated sesquiterpene lactones.

16368205
Menan H, Banzouzi JT, Hocquette A, Pelissier Y, Blache Y, Kone M, Mallie M, Assi LA, Valentin A
Antiplasmodial activity and cytotoxicity of plants used in West African traditional medicine for the treatment of malaria.
J Ethnopharmacol. 2005 Dec 17;.
Eighteen plants originating from Ivory Coast were selected by ethnobotanical survey as plants commonly used by traditional healers for the treatment of malaria. Extracts of these plants were tested on two strains of Plasmodium falciparum: FcM29-Cameroon (chloroquine-resistant strain) and a Nigerian chloroquine-sensitive strain. The powdered plants were used to prepare three kinds of extracts: by decoction in water, in ethanol (95%) and in pentane. A radioactive micromethod allowed the evaluation of the antiplasmodial in vitro activity of the extracts on P. falciparum. Concentrations inhibiting 50% of the parasite growth (IC(50)) ranged from 18mug/ml to more than 500mug/ml for aqueous and ethanol extracts and from 4.3mug/ml to more than 500mug/ml for pentane extracts. Cytotoxicity was estimated on A375 melanoma cells and a cytotoxicity/antiplasmodial index (CAR) was calculated for each extract, ranging from 1 to 10. The pentane extracts of Cola caricaefolia and Uvaria afzelii, which revealed the strongest antiplasmodial activity had CAR values of about 10.

12471433

Menezes CM, Kirchgatter K, Di Santi SM, Savalli C, Monteiro FG, Paula GA, Ferreira EI
In vitro chloroquine resistance modulation study on fresh isolates of Brazilian Plasmodium falciparum: intrinsic antimalarial activity of phenothiazine drugs.
Mem Inst Oswaldo Cruz. 2002 Oct;97(7):1033-9.
Phenothiazine drugs - fluphenazine, chlorpromazine, methotrimeprazine and trifluoperazine - were evaluated as modulating agents against Brazilian chloroquine-resistant fresh isolates of Plasmodium falciparum. Aiming to simulate therapeutic schedules, chloroquine was employed at the concentration used for sensitive falciparum malaria treatment and anti-psychotic therapeutic concentrations of the phenothiazine drugs were adopted in two-fold serial dilutions. The in vitro microtechnique for drug susceptibility was employed. Unlike earlier reported data, the phenothiazine modulating effect was not observed. However, all the drugs demonstrated intrinsic antiplasmodial activity in concentrations lower than those described in the literature. In addition, IC50 estimates have been shown to be inferior to the usual anti-psychotic therapeutic concentrations. Statistical analysis also suggested an increase in the parasitaemia rate or, even, a predominant antiparasitic effect of phenothiazine over chloroquine when used in combination.

12715057
Menezes CM, Kirchgatter K, Di Santi SM, Savalli C, Monteiro FG, Paula GA, Ferreira EI
In vitro evaluation of verapamil and other modulating agents in Brazilian chloroquine-resistant Plasmodium falciparum isolates.
Rev Soc Bras Med Trop. 2003 Jan-Feb;36(1):5-9. Epub 2003 Apr 22.
Verapamil, was assayed to record its modulating effect upon Brazilian Plasmodium falciparum isolates resistant to chloroquine. Other cardiovascular drugs known to be modulating agents in resistant malaria and/or multidrug-resistant neoplasias, including nifedipine, nitrendipine, diltiazem and propranolol, were also evaluated. Concentrations similar to those for cardiovascular therapy were used in the in vitro microtechnique for antimalarial drug susceptibility. Intrinsic antiplasmodial activity was observed from the lowest concentrations without a significant modulating action. Other reported modulating agents, such as the antipsychotic drug trifluoperazine and the antidepressants desipramine and imipramine, demonstrated similar responses under the same experimental conditions. Results suggest a much higher susceptibility of Brazilian strains, as well as an indifferent behaviour in relation to modulating agents.

12094310
Mitaine-Offer AC, Sauvain M, Deharo E, Munoz V, Zeches-Hanrot M
A new diterpene from Tanaecium jaroba.
Planta Med. 2002 Jun;68(6):568-9.
One new diterpene, 2 alpha-hydroxy-12beta-hydroxy-isopimara-8(14), 15-diene, and six known compounds as triterpenes, sterols and fatty acid, were isolated from the stem bark of Tanaecium jaroba (Bignoniaceae), a Bolivian plant used in traditional medicine. Their structures were established mainly by 1D and 2D NMR (COSY, HMQC, HMBC, ROESY) and their antiplasmodial activities were evaluated in vitro against Plasmodium falciparum.

11995947
Mitaine-Offer AC, Sauvain M, Valentin A, Callapa J, Mallie M, Zeches-Hanrot M
Antiplasmodial activity of aspidosperma indole alkaloids.
Phytomedicine. 2002 Mar;9(2):142-5.
The antiplasmodial activity of twelve alkaloids with an aspidospermane skeleton was estimated in vitro on chloroquine-resistant and sensitive strains of Plasmodium falciparum. Seven tetracyclic alkaloids possessing a free ethyl chain such aspidospermine, showed IC50 after incubation for 72 h between 3.2 and 15.4 microM. Moreover, four pentacyclic alkaloids with ethyl chain included in a tetrahydrofuran, such haplocine, showed a reduced activity, with IC50, after 72 h, between 22.6 and 52.6 microM. According to these results, a chloroquine-potentiating experiment was also performed with two of the most active compounds. Isobolograms were obtained and demonstrated a synergic effect of N-formyl-aspidospermidine and aspidospermine when associated with chloroquine. The cytotoxicity and the selectivity index of some alkaloids were also estimated.

12648820
Muregi FW, Chhabra SC, Njagi EN, Lang'at-Thoruwa CC, Njue WM, Orago AS, Omar SA, Ndiege IO
In vitro antiplasmodial activity of some plants used in Kisii, Kenya against malaria and their chloroquine potentiation effects.
J Ethnopharmacol. 2003 Feb;84(2-3):235-9.
Fifty-five organic and aqueous extracts of 11 plants used in malaria therapy in Kisii District, Kenya were tested in vitro against chloroquine (CQ)-sensitive and resistant strains of Plasmodium falciparum. Of the plants tested, 73% were active (IC(50) < 100 microg/ml). Three plants, Vernonia lasiopus, Rhamnus prinoides and Ficus sur afforded extracts with IC(50) values ranging less than 30 microg/ml against both CQ-

sensitive and resistant strains. Combination of some extracts with CQ against the multi-drug resistant P. falciparum isolate V1/S revealed some synergistic effect. The plant extracts with low IC(50) values may be used as sources for novel antimalarial compounds to be used alone or in combination with CQ.

12141852
Muriithi MW, Abraham WR, Addae-Kyereme J, Scowen I, Croft SL, Gitu PM, Kendrick H, Njagi EN, Wright CW
Isolation and in vitro antiplasmodial activities of alkaloids from Teclea trichocarpa: in vivo antimalarial activity and X-ray crystal structure of normelicopicine.
J Nat Prod. 2002 Jul;65(7):956-9.
Seven alkaloids have been isolated from Teclea trichocarpa including four, normelicopicine (1), arborinine (2), skimmianine (6), and dictamnine (7), that are reported for the first time in addition to the previously reported alkaloids melicopicine (3), tecleanthine (4), and 6-methoxytecleanthine (5). The structure of 1 was confirmed by single-crystal X-ray crystallography. Two alkaloids, 1 and 2, displayed limited in vitro activities against Plasmodium falciparum strains HB3 and K1, but there appeared to be little cross-resistance with chloroquine. Alkaloid 1 was found to have some activity against P. berghei in mice (32% suppression of parasitaemia at a dose of 25 mg x kg(-1) x day(-1)), but unlike chloroquine it did not inhibit beta-haematin formation in a cell-free system; 1 was found to have low in vitro cytotoxicity to KB cells (IC50 > 328 microM).

15225694
Musonda CC, Taylor D, Lehman J, Gut J, Rosenthal PJ, Chibale K
Application of multi-component reactions to antimalarial drug discovery. Part 1: Parallel synthesis and antiplasmodial activity of new 4-aminoquinoline Ugi adducts.
Bioorg Med Chem Lett. 2004 Aug 2;14(15):3901-5.
The synthesis of a new class of Ugi adducts incorporating the 4-aminoquinoline moiety is described. The novel compounds are active against both chloroquine-sensitive and chloroquine-resistant strains of Plasmodium falciparum with the best compound showing an IC(50) value of 73 nM against a resistant K1 strain.

11025150
Mustofa, Valentin A, Benoit-Vical F, Pelissier Y, Kone-Bamba D, Mallie M
Antiplasmodial activity of plant extracts used in west African traditional medicine.
J Ethnopharmacol. 2000 Nov;73(1-2):145-51.
Five plants originating from Ivory Coast were selected after an ethnobotanical survey, Alchornea cordifolia, Mitragyna inermis, Nauclea diderrichii, Pterocarpus santalinoides, and Terminalia glaucescens. Traditional healers for the treatment of malaria commonly used these plants. Extracts of these plants were tested on three strains of Plasmodium falciparum, FcB1-Colombia and FcM29-Cameroon (chloroquine-resistant strains) and a Nigerian chloroquine-sensitive strain. Extracts were obtained by preparing decoction in water of the powdered plant, the technique used by most of the traditional healers. A radioactive micromethod allowed the evaluation of the in vitro activity of the extracts on P. falciparum. Concentrations inhibiting 50% of the parasite growth (IC(50)) ranged from 2.34 to more than 500 microg/ml according to the plant. For the most active plants (A. cordifolia and T. glaucescens) ethanol and pentane extracts were made and tested. The IC(50) values obtained for these extracts ranged from 0.35 to 43.40 microg/ml. The stage specificity of the ethanol extracts of A. cordifolia and T. glaucescens and pentane extract of T. glaucescens on the parasite erythrocytic cycle were determined. The ethanol extract of T. glaucescens showed its highest activity at the transition from the trophozoite to the schizont stages. Cytotoxicity was estimated on human fibroblasts (HeLa) cells and a cytotoxicity/antiplasmodial index was calculated, it ranged between 5 and 21, and the best antiplasmodial extract (T. glaucescens ethanol extract) had the higher index (>20).

11120957
Nagaraj G, Uma MV, Shivayogi MS, Balaram H
Antimalarial activities of peptide antibiotics isolated from fungi.
Antimicrob Agents Chemother. 2001 Jan;45(1):145-9.
Malaria caused by Plasmodium falciparum is a major public health problem in the developing countries of the world. Clinical treatment of malaria has become complicated due to the occurrence of infections caused by drug resistant parasites. Secondary metabolites from fungi are an attractive source of chemotherapeutic agents. This work reports the isolation and in vitro antiplasmodial activities of peptide antibiotics of fungal origin. The three peptide antibiotics used in this study were efrapeptins, zervamicins, and antiamoebin. The high-performance liquid chromatography-purified peptides were characterized by nuclear magnetic resonance and mass spectral analysis. All three fungal peptides kill P. falciparum in culture with 50% inhibitory concentrations in the micromolar range. A possible mode of action of these peptide antibiotics on P. falciparum is presented.

16161998
Nguyen C, Kasinathan G, Leal-Cortijo I, Musso-Buendia A, Kaiser M, Brun R, Ruiz-Perez LM, Johansson NG, Gonzalez-Pacanowska D, Gilbert IH
Deoxyuridine triphosphate nucleotidohydrolase as a potential antiparasitic drug target.
J Med Chem. 2005 Sep 22;48(19):5942-54.
This paper describes a structure-activity study to identify novel, small-molecule inhibitors of the enzyme deoxyuridine 5'-triphosphate nucleotidohydrolase (dUTPase) from parasitic protozoa. The successful synthesis of a variety of analogues of dUMP is described in which the substituents are introduced at the 3'- and 5'-positions, together with variation in the heteroatom at the 5'-position. The compounds were assayed against recombinant Plasmodium falciparum and Leishmania major enzymes and the human enzyme to give a measure of selectivity. The compounds were also tested in vitro against the intact parasites P. falciparum and L. donovani. A number of potent and selective inhibitors of the P. falciparum dUTPase that show drug-like properties and represent good leads for future development were identified. The best inhibitors included the compounds 5'-tritylamino-2',5'-dideoxyuridine (2j) (Ki = 0.2 microM) and 5'-O-triphenylsilyl-2',3'-didehydro-2',3'-dideoxyuridine (5h) (Ki = 1.3 microM), with selectivity greater than 200-fold compared to the human enzyme. Structural features important for antiplasmodial activity were determined. The correlation observed between the inhibition of the enzyme and the inhibition of the parasite growth in vitro demonstrates that the P. falciparum dUTPase constitutes a valid and attractive novel target for the development of much-needed new antimalarial drugs.

11199137
Nilanonta C, Isaka M, Kittakoop P, Palittapongarnpim P, Kamchonwongpaisan S, Pittayakhajonwut D, Tanticharoen M, Thebtaranonth Y
Antimycobacterial and antiplasmodial cyclodepsipeptides from the insect pathogenic fungus Paecilomyces tenuipes BCC 1614.
Planta Med. 2000 Dec;66(8):756-8.
Bioassay-guided fractionation of the crude extract from the insect pathogenic fungus Paecilomyces tenuipes BCC 1614 led to the isolation and identification of two antimycobacterial and antiplasmodial cyclodepsipeptides, beauvericin and beauvericin A.

12428427
Nundkumar N, Ojewole JA
Studies on the antiplasmodial properties of some South African medicinal plants used as antimalarial remedies in Zulu folk medicine.
Methods Find Exp Clin Pharmacol. 2002 Sep;24(7):397-401.
The parasite lactate dehydrogenase (pLDH) assay method, a recently developed in vitro enzymatic method for evaluating antimalarial compounds, was used to examine the antiplasmodial activities of the aqueous leaf, stem-bark and fruit extracts of some plants used for the treatment and/or prophylaxis of malaria in KwaZulu-Natal province of South Africa. The in vitro antiplasmodial assay was carried out using a chloroquine-sensitive strain of malarial parasite, Plasmodium falciparum D10. A preliminary phytochemical analysis of the plant extracts was carried out using UV spectral analysis and thin-layer chromatography (TLC) to separate the chemical constituents of the extracts. Their chemical components were subsequently identified by treating the TLC plates with various spray reagents. Of the 14 plant extracts investigated, only 10 were found to have IC50 values of 10-50 micrograms/ml. The two most active extracts were Psidium guajava stem-bark extract and Vangueria infausta leaf extract, both of which showed IC50 values of 10-20 micrograms/ml. Phytochemical analysis of these two active plant extracts revealed the presence of anthraquinones, flavonoids, seccoirridoids and terpenoids.

11077169
Oketch-Rabah HA, Mwangi JW, Lisgarten J, Mberu EK
A new antiplasmodial coumarin from Toddalia asiatica roots.
Fitoterapia. 2000 Dec;71(6):636-40.
A new antiplasmodial coumarin, 5,7-dimethoxy-8-(3'-hydroxy-3'methyl-1'-butene)-coumarin (1), has been isolated from the roots of Toddalia asiatica. This finding supports the traditional use of this plant for the treatment of malaria.

15490799
Okpako LC, Ajaiyeoba EO
In vitro and in vivo antimalarial studies of Striga hermonthica and Tapinanthus sessilifolius extracts.
Afr J Med Med Sci. 2004 Mar;33(1):73-5.
The antimalarial activities of the methanol extracts of Striga hermonthica (whole plant) and Tapinanthus sessilifolius (leaves), commonly used in Northern Nigeria for the treatment of malaria, were evaluated. In the in vitro antiplasmodial analysis, the extracts of T. sessilifolius and S. hermonthica utilized in the study,

displayed mild to weak activities with IC50 values of 200.5 and 274.8 microg/ml respectively. This was investigated, using the multidrug resistant Plasmodium falciparum, K1 strain, in the parasite lactate dehydrogenase assay. The murine model in vivo antimalarial activity of the tested extracts, using chloroquine-sensitive Plasmodium berghei (ANKA P1), in the 4-day suppressive test, showed that both plants had intrinsic antimalarial properties, that were dose-dependent. At a dose of 400mg/kg weight of mice, extract of S. hermonthica exhibited a higher intrinsic antimalarial activity (68.5 % suppression) than that of T. sessilifolius (51.3 %). Chloroquine, the standard reference drug, had an average suppression of 78.0 % at a dose of 10 mg/kg weight of mice while normal saline was used as control. Preliminary phytochemical screening of the extracts indicated the presence ofsaponins, tannins, flavonoids, volatile oils and cardiac glycosides.

12820239
Okunade AL, Bikoff RE, Casper SJ, Oksman A, Goldberg DE, Lewis WH
Antiplasmodial activity of extracts and quassinoids isolated from seedlings of Ailanthus altissima (Simaroubaceae).
Phytother Res. 2003 Jun;17(6):675-7.
Extracts and isolated compounds from seedlings of Ailanthus altissima, were assessed for antiplasmodial activity in vitro. Two quassinoids, ailanthone and 6alpha-tigloyloxychaparrinone, isolated from the active extracts showed activity against both chloroquine-resistant and chloroquine-sensitive strains of Plasmodium falciparum in vitro. Only ailanthone demonstrated low toxicity against the Vero cell line (kidney cells from the African green monkey). This is the first report of the isolation and antiplasmodial activity of 6alpha-tigloyloxychaparrinone from this species.

15158990
Okunade AL, Lewis WH
Oleanene constituents of Lantana cujabensis.
Fitoterapia. 2004 Jun;75(3-4):327-31.
A new compound, 3beta,25-epoxy-3alpha-hydroxy-22beta-isobutanoyloxyolean-12-ene-28-oic acid (1), and two known triterpenoids lantanilic acid (2) and camaric acid (3) were isolated from the stem and leaves of Lantana cujabensis. Their structures were elucidated by spectroscopic methods. The ethanol extracts did not show significant in vitro antiplasmodial activity against chloroquine-sensitive or resistant strains of Plasmodium falciparum.

11985850
Onegi B, Kraft C, Kohler I, Freund M, Jenett-Siems K, Siems K, Beyer G, Melzig MF, Bienzle U, Eich E
Antiplasmodial activity of naphthoquinones and one anthraquinone from Stereospermum kunthianum.
Phytochemistry. 2002 May;60(1):39-44.
A lipophilic extract of the root bark of Stereospermum kunthianum revealed antiplasmodial activity in vitro. Bioassay-guided fractionation led to the isolation of four novel naphthoquinones (sterekunthals A and B, pyranokunthones A and B) and one novel anthraquinone (anthrakunthone) together with the known naphthoquinone pinnatal. The structures of the novel compounds were determined by comprehensive analyses of their 1D and 2D NMR data. The antiplasmodial activities and toxicity against the endothelial cell line ECV-304 of the isolated compounds have been assessed.

15801861
Onyeibor O, Croft SL, Dodson HI, Feiz-Haddad M, Kendrick H, Millington NJ, Parapini S, Phillips RM, Seville S, Shnyder SD, Taramelli D, Wright CW
Synthesis of some cryptolepine analogues, assessment of their antimalarial and cytotoxic activities, and consideration of their antimalarial mode of action.
J Med Chem. 2005 Apr 7;48(7):2701-9.
A series of analogues of cryptolepine (1) have been synthesized and evaluated for their in vitro antiplasmodial and cytotoxic properties. The IC(50) values of several compounds (11a, 11k-m, 11o, 13) against Plasmodium falciparum (strain K1) were 90% at doses of 25 mg kg(-1) day(-1) with no apparent toxicity to the mice. 2,7-Dibromocryptolepine (15) was evaluated at several dose levels, and a dose-dependent suppression of parasitemia was seen (ED(90) = 21.6 mg kg(-1) day(-1)). The antimalarial mode of action of 1 appears to be similar to that of chloroquine and involves the inhibition of hemozoin formation. A number of analogues were assessed for their effects on the inhibition of beta-hematin (hemozoin) formation, and the results were compared with their antiplasmodial activities having taken account of their predicted accumulation into the acidic parasite food vacuole. No correlation was seen (r(2) = 0.0781) suggesting that the potent antimalarial activity of compounds such as 15 involves other mechanisms in addition to the inhibition of hemozoin formation.

16252918

Ospina CA, Rodriguez AD, Sanchez JA, Ortega-Barria E, Capson TL, Mayer AM
Caucanolides A-F, unusual antiplasmodial constituents from a colombian collection of the gorgonian coral Pseudopterogorgia bipinnata.
J Nat Prod. 2005 Oct;68(10):1519-26.
Six new diterpenoids, caucanolides A-F (1-6), have been isolated from extracts of the gorgonian octocoral Pseudopterogorgia bipinnata collected near the Colombian Southwestern Caribbean Sea. The structures of 1-6 were elucidated by comprehensive analysis of spectroscopic data. The caucanolides showed in vitro antiplasmodial activity against the malaria parasite, Plasmodium falciparum. In addition to possessing structures based on novel carbon skeletons, one of these metabolites, caucanolide B (2), constitutes the only example from nature of a secondary metabolite possessing the N(1),N(1)-dimethyl-N(2)-acylformamidine functionality.

11052082
Osterhage C, Kaminsky R, Konig GM, Wright AD
Ascosalipyrrolidinone A, an antimicrobial alkaloid, from the obligate marine fungus Ascochyta salicorniae.
J Org Chem. 2000 Oct 6;65(20):6412-7.
From the green alga Ulva sp., the endophytic and obligate marine fungus Ascochyta salicorniae was isolated. A. salicorniae was mass cultivated and found to produce the unprecedented and structurally unusual tetramic acid containing metabolites ascosalipyrrolidinones A (1) and B (2). Additionally, the new natural product ascosalipyrone (3) and the known metabolites 4 and 5 were obtained. Ascosalipyrrolidinone A (1) has antiplasmodial activity toward Plasmodium falciparum strains K1 and NF 54, as well as showing antimicrobial activity and inhibiting tyrosine kinase p56lck.

11908970
Osterhage C, Konig GM, Holler U, Wright AD
Rare sesquiterpenes from the algicolous fungus Drechslera dematioidea.
J Nat Prod. 2002 Mar;65(3):306-13.
From the inner tissue of the marine red alga Liagora viscida the fungus Drechslera dematioidea was isolated. After mass cultivation, the fungus was investigated for its secondary metabolite content, and 10 new sesquiterpenoids [isosativenetriol (1), drechslerines A (2) and B (3), 9-hydroxyhelminthosporol (5), drechslerines C-G (6-10), and sativene epoxide (12)] were isolated. Compounds 8 and 10 exhibited antiplasmodial activity against Plasmodium falciparum strains K1 and NF54. The known compounds helminthosporol (4), cis-sativenediol (11), isocochlioquinone A (14), isocochlioquinone C (15), and cochlioquinone B (16) were also isolated. All structures were elucidated using spectroscopic methods, mainly 1D and 2D NMR and MS.

15996841
Otshudi AL, Apers S, Pieters L, Claeys M, Pannecouque C, De Clercq E, Van Zeebroeck A, Lauwers S, Frederich M, Foriers A
Biologically active bisbenzylisoquinoline alkaloids from the root bark of Epinetrum villosum.
J Ethnopharmacol. 2005 Oct 31;102(1):89-94.
Methanol and water extracts of the root of Epinetrum villosum (Exell) Troupin (Menispermaceae) were found to exhibit antimicrobial and antiplasmodial activities. Investigation of the active methanol fraction led to the isolation of four bisbenzylisoquinoline alkaloids, i.e., cycleanine, cycleanine N-oxide, isochondodendrine and cocsoline. Structures were established by spectroscopic methods. Cocsoline displayed antibacterial and antifungal activities (MIC values of 1000-15.62 and 31.25 microg/ml, respectively). Isochondodendrine was found to have the most potent antiplasmodial activity (IC50 = 0.10 microg/ml), whereas the IC50 on HCT-116 human colon carcinoma cells was 17.5 microg/ml (selectivity index 175). Cycleanine acted against HIV-2 (EC50=1.83 microg/ml) but was at least 10-fold less active against HIV-1. Cycleanine N-oxide showed no activity towards all tested microorganisms.

15922377
Ozipek M, Donmez AA, Calis I, Brun R, Ruedi P, Tasdemir D
Leishmanicidal cycloartane-type triterpene glycosides from Astragalus oleifolius.
Phytochemistry. 2005 May;66(10):1168-73.
Two new cycloartane-type glycosides oleifoliosides A (1) and B (2) were isolated from the lower stem parts of Astragalus oleifolius. Their structures were identified as 3-O-[beta-xylopyranosyl-(1 --> 2)-alpha-arabinopyranosyl]-6-O-beta-xylopyranosyl-3beta,6alpha,16beta,24(S),25-pentahydroxycycloartane and 3-O-[beta-xylopyranosyl-(1 --> 2)-alpha-arabinopyranosyl]-6-O-beta-glucopyranosyl-3beta,6alpha,16beta,24(S),25-pentahydroxycycloartane, respectively, by means of spectroscopic methods (IR, 1D and 2D NMR, ESI-MS). Three known cycloartane glycosides cyclocanthoside E (3), astragaloside II (4) and astragaloside IV (5) were also isolated and characterized. All five compounds were evaluated for in vitro trypanocidal, leishmanicidal and antiplasmodial activities as well as their cytotoxic potential on primary mammalian (L6)

cells. Except for the compound 5, all compounds showed notable growth inhibitory activity against Leishmania donovani with IC50 values ranging from 13.2 to 21.3 microg/ml. Only weak activity against Trypanosoma brucei rhodesiense was observed with the known compounds astragaloside II (4, IC50 66.6 microg/ml) and cyclocanthoside E (3, IC50 85.2 microg/ml), while all compounds were inactive against Trypanosoma cruzi and Plasmodium falciparum. None of the compounds were toxic to mammalian cells (IC50's > 90 microg/ml). This is the first report of leishmanicidal and trypanocidal activity of cycloartane-type triterpene glycosides.

10705730
Paulo A, Gomes ET, Steele J, Warhurst DC, Houghton PJ
Antiplasmodial activity of Cryptolepis sanguinolenta alkaloids from leaves and roots.
Planta Med. 2000 Feb;66(1):30-4.
The roots of Cryptolepis sanguinolenta have been investigated for their chemical composition since 1931 but so far no studies on the leaves have been reported although they are used in traditional medicine in Guinea-Bissau. Two new alkaloids identified as cryptolepinoic acid (1) and methyl cryptolepinoate (2) and the known alkaloids cryptolepine (4), hydroxycryptolepine (5/5a) and quindoline (6), were isolated from the ethanolic and chlorophormic leaf extracts. Aqueous and ethanolic extracts of the leaves and roots and seven alkaloids isolated from those extracts were tested in vitro against Plasmodium falciparum K1 (multidrug-resistant strain) and T996 (chloroquine-sensitive clone). All the extracts were shown to give 90% inhibition of P. falciparum K1 growth at concentrations < 23 micrograms/ml. Cryptolepine (4) was the most active alkaloid tested with IC50 values (0.23 microM to K1; 0.059 microM to T996) comparable with chloroquine (0.26 microM to K1; 0.019 microM to T996). The indolobenzazepine alkaloid cryptoheptine (7) was the second most active with IC50 values of 0.8 microM (K1) and 1.2 microM (T996). Cryptolepinoic acid (1) showed no significant activity while its ethyl ester derivative 3 was active against P. falciparum K1 (IC50 = 3.7 microM). All the indoloquinoline alkaloids showed cross-resistance with chloroquine but not the indolobenzazepine alkaloid 7. It was noticed that alkaloids with weakly basic characteristics were active whereas other structurally related alkaloids with different acid-base profiles were inactive. These observations are in agreement with the antimalarial mechanism of action for quinolines.

10456963
Perkins DJ, Kremsner PG, Schmid D, Misukonis MA, Kelly MA, Weinberg JB
Blood mononuclear cell nitric oxide production and plasma cytokine levels in healthy gabonese children with prior mild or severe malaria.
Infect Immun. 1999 Sep;67(9):4977-81.
Plasmodium falciparum malaria is an important cause of morbidity and mortality in children. Factors that determine the development of mild versus severe malaria are not fully understood. Since host-derived nitric oxide (NO) has antiplasmodial properties, we measured NO production and NO synthase (NOS) activity in peripheral blood mononuclear cells (PBMC) from healthy Gabonese children with a history of prior mild malaria (PMM) or prior severe malaria (PSM) caused by P. falciparum. The PMM group had significantly higher levels of NOS activity in freshly isolated PBMC and higher NO production and NOS activity in cultured PBMC. The investigation of NO-modulating cytokines (e.g., interleukin 12, gamma interferon, tumor necrosis factor alpha [TNF-alpha], and transforming growth factor beta1) as an explanation for differing levels of NOS activity revealed that plasma levels of TNF-alpha were significantly higher in the PSM group. Our results suggest that NOS/ NO and TNF-alpha are markers for prior disease severity and important determinants of resistance to malaria.

11037780
Perlmann P, Perlmann H, Looareesuwan S, Krudsood S, Kano S, Matsumoto Y, Brittenham G, Troye-Blomberg M, Aikawa M
Contrasting functions of IgG and IgE antimalarial antibodies in uncomplicated and severe Plasmodium falciparum malaria.
Am J Trop Med Hyg. 2000 Mar;62(3):373-7.
Plasmodial infection results in a significant elevation of the blood concentrations of immunoglobulins including IgE. Two well-characterized groups of adult Thai patients with either uncomplicated or severe Plasmodium falciparum malaria were studied over a period of four weeks. The mean parasitemias were approximately three-fold higher in patients with severe malaria than in those with uncomplicated disease. The mean concentrations of both total IgG and IgG antiplasmodial antibodies tended to be highest in the group with uncomplicated disease while total IgE and IgE antibodies were higher in the group with severe disease. The IgE antibodies detected in approximately 65% of the patients were positively correlated to parasitemia. These results suggest that antiplasmodial IgG antibodies are involved in reducing the severity of P. falciparum malaria, while IgE antibodies may contribute to the pathogenesis of this infection.

15740892

Philippe G, Angenot L, De Mol P, Goffin E, Hayette MP, Tits M, Frederich M
In vitro screening of some Strychnos species for antiplasmodial activity.
J Ethnopharmacol. 2005 Mar 21;97(3):535-9.
The antiplasmodial activity of crude extracts of 19 species of Strychnos (Loganiaceae) was assessed in vitro against a chloroquine-susceptible strain of Plasmodium falciparum. For each species, ethyl acetate (EtOAc) extracts were analysed and, for the most active species, methanolic (MeOH) extracts were also tested. Among them, Strychnos variabilis De Wild. seemed to be very promising (inhibitory concentration 50% (IC50) < 5 microg/ml) whereas two other species, Strychnos gossweileri Exell and Strychnos mellodora S. Moore, could be interesting (IC50 < 15 microg/ml) in further antimalarial studies.

12560037
Philippe G, De Mol P, Zeches-Hanrot M, Nuzillard JM, Tits MH, Angenot L, Frederich M
Indolomonoterpenic alkaloids from Strychnos icaja roots.
Phytochemistry. 2003 Feb;62(4):623-9.
In the course of our search for new antiplasmodial alkaloids from Strychnos icaja, we have isolated five alkaloids: three monomers, protostrychnine and genostrychnine, previously described in Strychnos nux-vomica, pseudostrychnine, already found in the leaves of the plant, a new bisindolic alkaloid, named strychnogucine C, and the first naturally occurring trimeric indolomonoterpenic alkaloid: strychnohexamine. This latter trimeric alkaloid presented an antiplasmodial activity against the FCA Plasmodium falciparum line near 1 microM.

16375888
Philippe G, Nguyen L, Angenot L, Frederich M, Moonen G, Tits M, Rigo JM
Study of the interaction of antiplasmodial strychnine derivatives with the glycine receptor.
Eur J Pharmacol. 2006 Jan 13;530(1-2):15-22. Epub 2005 Dec 20.
Strychnos icaja Baill. (Loganiaceae) is a liana found in Central Africa known to be an arrow and ordeal poison but also used by traditional medicine to treat malaria. Recently, many dimeric or trimeric indolomonoterpenic alkaloids with antiplasmodial properties have been isolated from its rootbark. Since these alkaloids are derivatives of strychnine, it was important, in view of their potential use as antimalarial drugs, to assess their possible convulsant strychnine-like properties. In that regard, their interaction with the strychnine-sensitive glycine receptor was investigated by whole-cell patch-clamp recordings on glycine-gated currents in mouse spinal cord neurons in culture and by [(3)H]strychnine competition assays on membranes from adult rat spinal cord. These experiments were carried out on sungucine (leading compound of the chemical class) and on the antiplasmodial strychnogucine B (dimeric) and strychnohexamine (trimeric). In comparison with strychnine, all compounds interact with a very poor efficacy and only at concentrations >1 microM with both [(3)H]strychnine binding and glycine-gated currents. Furthermore, the effects of strychnine and protostrychnine, a monomeric alkaloid (without antiplasmodial activity) also isolated from S. icaja and differing from strychnine only by a cycle opening, were compared in the same way. The weak interaction of protostrychnine confirms the importance of the G cycle ring structure in strychnine for its binding to the glycine receptor and its antagonist properties.

10640763
Pied S, Roland J, Louise A, Voegtle D, Soulard V, Mazier D, Cazenave PA
Liver CD4-CD8- NK1.1+ TCR alpha beta intermediate cells increase during experimental malaria infection and are able to exhibit inhibitory activity against the parasite liver stage in vitro.
J Immunol. 2000 Feb 1;164(3):1463-9.
Experimental infection of C57BL/6 mice by Plasmodium yoelii sporozoites induced an increase of CD4-CD8- NK1.1+ TCR alpha beta int cells and a down-regulation of CD4+ NK1.1+ TCR alpha beta int cells in the liver during the acute phase of the infection. These cells showed an activated CD69+, CD122+, CD44high, and CD62Lhigh surface phenotype. Analysis of the expressed TCRV beta segment repertoire revealed that most of the expanded CD4-CD8- (double-negative) T cells presented a skewed TCRV beta repertoire and preferentially used V beta 2 and V beta 7 rather than V beta 8. To get an insight into the function of expanded NK1.1+ T cells, experiments were designed in vitro to study their activity against P. yoelii liver stage development. P. yoelii-primed CD3+ NK1.1+ intrahepatic lymphocytes inhibited parasite growth within the hepatocyte. The antiplasmodial effector function of the parasite-induced NK1.1+ liver T cells was almost totally reversed with an anti-CD3 Ab. Moreover, IFN-gamma was in part involved in this antiparasite activity. These results suggest that up-regulation of CD4-CD8- NK1.1+ alpha beta T cells and down-regulation of CD4+ NK1.1+ TCR alpha beta int cells may contribute to the early immune response induced by the Plasmodium during the prime infection.

16452619
Pimentel C, Choi SJ, Chagot B, Guette C, Camadro JM, Darbon H
Solution structure of PcFK1, a spider peptide active against Plasmodium falciparum.

Protein Sci. 2006 Mar;15(3):628-34. Epub 2006 Feb 1.
Psalmopeotoxin I (PcFK1) is a 33-amino-acid residue peptide isolated from the venom of the tarantula Psalmopoeus cambridgei. It has been recently shown to possess strong antiplasmodial activity against the intra-erythrocyte stage of Plasmodium falciparum in vitro. Although the molecular target for PcFK1 is not yet determined, this peptide does not lyse erythrocytes, is not cytotoxic to nucleated mammalian cells, and does not inhibit neuromuscular function. We investigated the structural properties of PcFK1 to help understand the unique mechanism of action of this peptide and to enhance its utility as a lead compound for rational development of new antimalarial drugs. In this paper, we have determined the three-dimensional solution structure by (1)H two-dimensional NMR means of recombinant PcFK1, which is shown to belong to the ICK structural superfamily with structural determinants common to several neurotoxins acting as ion channels effectors.

12451493
Pittayakhajonwut P, Theerasilp M, Kongsaeree P, Rungrod A, Tanticharoen M, Thebtaranonth Y
Pughiinin A, a sesquiterpene from the fungus Kionochaeta pughii BCC 3878.
Planta Med. 2002 Nov;68(11):1017-9.
A novel secondary metabolite, pughiinin A, together with pycnidione, mevalonolactone, and 7-hydroxy-2-methylchromanone, was isolated from the seed fungus Kionochaeta pughii BCC 3878. The chemical structure was established by spectroscopic methods and by single crystal X-ray crystallography. Pughiinin A and pycnidione exhibited in vitro antiplasmodial activity against Plasmodium falciparum (K1 strain). Pycnidione also showed anti-cancer activity against KB and BC cell lines with the IC 50 values of 2.0 and 1.6 microg/mL, respectively.

11448545
Prozesky EA, Meyer JJ, Louw AI
In vitro antiplasmodial activity and cytotoxicity of ethnobotanically selected South African plants.
J Ethnopharmacol. 2001 Aug;76(3):239-45.
The resistance of Plasmodium spp. to currently used drugs has become a serious problem and efforts are being directed in obtaining new drugs with different structural features. One option favoured is the search for new plant derived antimalarial drugs. Bark and leaves of 20 extracts from 14 South African plant species were tested for in vitro antiplasmodial activity by means of the flow cytometric test. The most active extract of each species giving more than 70% inhibition at 50 microg/ml was selected for determination of IC(50) values. Two extracts had IC(50) values below 2 microg/ml, another seven had IC(50) values between 2 and 5 microg/ml while one had an IC(50) of 10.1 microg/ml. Chloroquine had an IC(50) of 0.043 microg/ml. Cytotoxicities of the five most active extracts at 50 microg/ml were determined with the monkey kidney cell toxicity test and the ID(50) values ranged between 35 and 100 microg/ml.

10704934
Rafatro H, Ramanitrahasimbola D, Rasoanaivo P, Ratsimamanga-Urverg S, Rakoto-Ratsimamanga A, Frappier F
Reversal activity of the naturally occurring chemosensitizer malagashanine in Plasmodium malaria.
Biochem Pharmacol. 2000 May 1;59(9):1053-61.
Malagashanine (MG) is the parent compound of a new type of indole alkaloids, the N(b)C(21)-secocuran, isolated so far from the Malagasy Strychnos species traditionally used as chloroquine adjuvants in the treatment of chronic malaria. Previously, it was shown to have weak in vitro intrinsic antiplasmodial activity (IC(50) = 146.5 +/- 0.2 microM), but did display marked in vitro chloroquine-potentiating action against the FcM29 chloroquine-resistant strain of Plasmodium falciparum. The purpose of the present study was to further investigate its reversal activity. Thus, the previous in vitro results were tested in vivo. The interaction of MG with several antimalarials against various strains of P. falciparum was also assessed. As expected, MG enhanced the effect of chloroquine against the resistant strain W2, but had no action on the susceptible strain 3D7 and two sensitive isolates. Interestingly, MG was found to exhibit significant chloroquine-potentiating action against the FcB1 strain formerly described as a resistant strain but one which has since lost its resistance for unknown reasons. One other relevant result that arose from our study was the observation of the selective enhancing action of MG on quinolines (chloroquine, quinine, and mefloquine), aminoacridines (quinacrine and pyronaridine), and a structurally unrelated drug (halofantrine), all of which are believed to exert their antimalarial effect by binding with haematin. MG was finally found to specifically act with chloroquine on the old trophozoite stage of the P. falciparum cycle. Similarities and differences between verapamil and MG reversal activity are briefly presented.

15332710
Rakotomanga M, Razakantoanina V, Raynaud S, Loiseau PM, Hocquemiller R, Jaureguiberry G
Antiplasmodial activity of acetogenins and inhibitory effect on Plasmodium falciparum adenylate translocase.
J Chemother. 2004 Aug;16(4):350-6.

Three Annonaceous acetogenins exhibited in vitro antimalarial activities on a chloroquine-resistant Plasmodium falciparum strain, with IC50s ranging from 5 to 10 microM. Structure-activity relationships showed that maximal antimalarial activity occurred in the presence of at least one tetrahydrofuran moiety and a synergistic action with chloroquine was observed. These acetogenins partially inhibited the P. falciparum adenylate translocase.

15921436
Ramanandraibe V, Martin MT, Rakotondramanana DL, Mambu L, Ramanitrahasimbola D, Labaied M, Grellier P, Rasoanaivo P, Frappier F
Pseudoguanolide sesquiterpene lactones from Vernoniopsis caudata and their in vitro antiplasmodial activities.
J Nat Prod. 2005 May;68(5):800-3.
Two new helenanolide sesquiterpene lactones, 1 and 2, as well as one known related structure, 11alpha,13-dihydrohelenalin-[2-(1-hydroxyethyl)acrylate] (3), together with 4'-beta-d-O-glucopyranosyl-luteolin and ethyl 2,5-dihydroxycinnamate were isolated from an ethyl acetate extract of leaves of Vernoniopsis caudatawith potent antiplasmodial activity (IC50 1.6 microg/mL) in a preliminary biological screen. The structures of the new compounds were determined by spectroscopic techniques. The three sesquiterpene lactones 1-3 displayed strong in vitro antiplasmodial activity, with IC50 values of 1, 0.19, and 0.41 microM, respectively. However, these compounds also exhibited considerable cytotoxicity on KB cells (IC50 < 1 microM in each case).

11180519
Ramanitrahasimbola D, Rasoanaivo P, Ratsimamanga-Urverg S, Federici E, Palazzino G, Galeffi C, Nicoletti M
Biological activities of the plant-derived bisindole voacamine with reference to malaria.
Phytother Res. 2001 Feb;15(1):30-3.
The in vivo antiplasmodial activity of voacamine was assessed in a 4-day test. It was shown to exhibit in vivo activity with 25.4% and 43.4% inhibition of parasitaemia with 2.5 and 10 mg/kg, respectively. In synchronized cultures, it was found to act on trophozoite and schizont stages of Plasmodium falciparum. Using the FMC29 strain of Plasmodium falciparum as parasite and the isobologram curve as a method to assess interaction in drug combination, it was shown to lack any chloroquine-enhancing activity and its in vitro antiplasmodial effect was not potentiated by the chemosensitizer malagashanine. Copyright -Copyright 2001 John Wiley & Sons, Ltd.

15991834
Randrianarivelojosia M, Jambou R
Isradipine--a calcium channel blocker--does not potentiate chloroquine antiplasmodial activity against Plasmodium falciparum.
Parasite. 2005 Jun;12(2):187-9.
Culturing fresh clinical isolates of P. falciparum and using the isotopic method, we tested separately chloroquine and isradipine--a calcium channel blocker--, and also the combination isradipine plus chloroquine. Tested wild isolates were chloroquine-sensitive. With regard to the combination isradipine/chloroquine, the isobolograms obtained indicate that isradipine antagonises chloroquine antiplasmodial activity. Taking into account these findings, we discuss the issues related to the calcium channel blocker molecules.

12921540
Randrianarivelojosia M, Rasidimanana VT, Rabarison H, Cheplogoi PK, Ratsimbason M, Mulholland DA, Mauclere P
Plants traditionally prescribed to treat tazo (malaria) in the eastern region of Madagascar.
Malar J. 2003 Jul 24;2:25. Epub 2003 Jul 24.
BACKGROUND: Malaria is known as tazo or tazomoka in local terminology in Madagascar. Within the context of traditional practice, malaria (and/or malaria symptoms) is commonly treated by decoctions or infusions from bitter plants. One possible approach to the identification of new antimalarial drug candidates is to search for compounds that cure or prevent malaria in plants empirically used to treat malaria. Thus, it is worth documenting the ethnobotanical data, and testing the antiplasmodial activity of the extractive from plants. METHODS: We interviewed traditional healers, known locally as ombiasy, at Andasibe in the eastern, rainy part of Madagascar. We recorded details of the preparation and use of plants for medicinal purposes. We extracted five alkaloids from Z. tsihanimposa stem bark, and tested them in vitro against Plasmodium falciparum FCM29. RESULTS: We found that traditional healers treat malaria with herbal remedies consisting of one to eight different plants. We identified and listed the medicinal plants commonly used to treat malaria. The plants used included a large number of species from different families. Zanthoxylum sp (Rutaceae) was frequently cited, and plants from this genus are also used to treat malaria in other parts of

Madagascar. From the plant list, Zanthoxylum tsihanimposa, bitter plant endemic to Madagascar, was selected and examined. Five alkaloids were isolates from the stem bark of this plant, and tested in vitro against malaria parasite. The geometric mean IC50 values ranged from 98.4 to 332.1 micromolar. The quinoline alkaloid gamma-fagarine exhibited the strongest antiplasmodial activity. CONCLUSIONS: The current use of plants for medicinal purposes reflects the attachment of the Malagasy people to their culture, and also a lack of access to modern medicine. The possible extrapolation of these in vitro findings, obtained with plant extracts, to the treatment of malaria and/or the signs evoking malaria is still unclear. If plants are to be used as sources of novel antimalarial compounds, we need to increase our knowledge of their empirical use to improve plant selection. In the hope of preserving useful resources, we should now gather and record ethnobotanical data in Madagascar, and should try to bridge the gaps between empirics and realism.

15478200
Rasoanaivo P, Ramanitrahasimbola D, Rafatro H, Rakotondramanana D, Robijaona B, Rakotozafy A, Ratsimamanga-Urverg S, Labaied M, Grellier P, Allorge L, Mambu L, Frappier F
Screening extracts of Madagascan plants in search of antiplasmodial compounds.
Phytother Res. 2004 Sep;18(9):742-7.
One hundred and ninety plants, of which 51 are used to treat malaria in traditional medicine, were collected in five different ecosystems of Madagascar for a screening programme devoted to the search of naturally-occurring antimalarial compounds. Thirty-nine plants, of which 12 are used as herbal antimalarials, were found to display in vitro activity against Plasmodium falciparum with a median inhibitory concentration (IC50) lower than 5 microg/ml while 9 had an IC50 ranging from 5 to 7.5 microg/ml. Seventeen of them exhibited cytotoxic effects on murine P388 leukemia cells with an IC50 < 10 microg/ml. The biological activities were mostly located in the ethyl acetate fractions. Bioassay-directed fractionation is underway to isolate the active constituents.

15686950
Razafimahefa D, Pelinski L, Martin MT, Ramanitrahasimbola D, Rasoanaivo P, Brocard J
Synthesis and chloroquine-enhancing activity of Na-deacetyl-ferrocenoyl-strychnobrasiline.
Bioorg Med Chem Lett. 2005 Feb 15;15(4):1239-41.
Several strychnobrasiline derivatives have been synthesized to overcome the lack of in vivo reversal activity of the parent compound. In the present study, N(a)-deacetyl-ferrocenoyl-strychnobrasiline was synthesized by condensing N(a)-deacetyl-strychnobrasiline with ferrocenic acid previously treated with oxalyl chloride. While the in vitro antiplasmodial activity of the test compound (IC(50)=4.83 microg/mL) was increased 15-fold compared to that of strychnobrasiline, and the in vitro enhancing activity was found to be similar to that of the parent compound, the compound was devoid of any in vivo potentiating effect, and an antagonistic effect was even observed at higher doses. Based on the overall results on the hemisynthesis of strychnobrasiline derivatives for better reversal activity, this strategy has appeared to be of little value for useful drugs.

15125962
Romeo S, Dell'Agli M, Parapini S, Rizzi L, Galli G, Mondani M, Sparatore A, Taramelli D, Bosisio E
Plasmepsin II inhibition and antiplasmodial activity of Primaquine-Statine 'double-drugs'.
Bioorg Med Chem Lett. 2004 Jun 7;14(11):2931-4.
Statine-based inhibitors of Plasmepsin II (PLMII) coupled with Primaquine have been designed using the 'double-drug' approach. The IC50 values for PLMII inhibition ranged from 0.59 to 400 nM and the best IC50 value for inhibition of Plasmodium falciparum growth in vitro was 0.4 microM, which represent a remarkable improvement compared to other statine-based PLMII inhibitors.

16124784
Ross SA, Al-Azeib MA, Krishnaveni KS, Fronczek FR, Burandt CL
Alkamides from the leaves of Zanthoxylum syncarpum.
J Nat Prod. 2005 Aug;68(8):1297-9.
Three alkamides (1-3) were isolated from the leaves of Zanthoxylum syncarpum. The structures of the new compounds 1 and 2 were established by spectroscopic data and chemical conversion, and by the X-ray crystallography of 1. Compound 3, the racemic form of the known compound syncarpamide, showed moderate antiplasmodial activity, with IC50 values of 4.2 and 6.1 microM against Plasmodium falciparum D6 clone and W2 clone, respectively.

14738394
Ross SA, Sultana GN, Burandt CL, ElSohly MA, Marais JP, Ferreira D
Syncarpamide, a new antiplasmodial (+)-norepinephrine derivative from Zanthoxylum syncarpum.
J Nat Prod. 2004 Jan;67(1):88-90.

A new (+)-norepinephrine derivative, syncarpamide (1), along with a known coumarin, (+)-S-marmesin (2), and one known alkaloid, decarine (3), have been isolated from the stem of Zanthoxylum syncarpum. The structure of compound 1 was elucidated on the basis of 1D and 2D NMR, MS, IR, optical rotation, and CD analyses. Its absolute stereochemistry was elucidated by synthesis of its enantiomer and subsequent comparison of CD data. Characterizations of compounds 2 and 3 were based on spectral analysis and comparison with reported data. Compounds 1 and 3 showed antiplasmodial activity, with IC(50) values of 2.04 and 1.44 microM against Plasmodium falciparum D(6) clone and 3.06 and 0.88 microM against P. falciparum W(2) clone, respectively. Compound 3 showed cytotoxicity at 56.42 microM, whereas compound 1 was not cytotoxic at 10.42 microM. Compound 1 was tested for hypotensive activity, but no activity was observed. Compound 2 showed no antiplasmodial or antimicrobial activities.

12916053
Rucker G, Manns D, Schenkel EP, Hartmann R, Heinzmann BM
A triterpene ozonide from Senecio selloi.
Arch Pharm (Weinheim). 2003 Jul;336(4-5):205-7.
From the dried and fresh aerial parts of Senecio selloi Spreng, De Candolle (Asteraceae), the new triterpene ozonide 1 was isolated. Its structure was elucidated by NMR experiments, including inverse techniques HMQC and HMBC and by synthesis from the precursor 2 In contrast to natural peroxides, no antiplasmodial activity was detected for the ozonide 1.

15234750
Rukachaisirikul T, Siriwattanakit P, Sukcharoenphol K, Wongvein C, Ruttanaweang P, Wongwattanavuch P, Suksamrarn A
Chemical constituents and bioactivity of Piper sarmentosum.
J Ethnopharmacol. 2004 Aug;93(2-3):173-6.
Eight amides, pellitorine (1), guineensine (2), brachystamide B (3), sarmentine (4), brachyamide B (5), 1-piperettyl pyrrolidine (6), 3',4',5'-trimethoxycinnamoyl pyrrolidine (7) and sarmentosine (8), two lignans, (+)-asarinin (9) and sesamin (10), and four other compounds, 1-(3,4-methylenedioxyphenyl)-1E-tetradecene (11), methyl piperate (12) and a mixture of beta-sitosterol (13) and stigmasterol (14), were isolated from the fruits of Piper sarmentosum (Piperaceae). This is the first reported isolation of compounds 2, 3, 5, 6, 7, 9, 10 and 12 from this plant species. Their structures were established from spectral data. These compounds were evaluated in antituberculosis and antiplasmodial tests. The results showed that compounds 4 and 6 exhibited both activities while compounds 1, 2, 5, 8 and 11 showed only antituberculosis activity. This is the first report of the antituberculosis and antiplasmodial activities for these compounds.

10904174
Saidu K, Onah J, Orisadipe A, Olusola A, Wambebe C, Gamaniel K
Antiplasmodial, analgesic, and anti-inflammatory activities of the aqueous extract of the stem bark of Erythrina senegalensis.
J Ethnopharmacol. 2000 Jul;71(1-2):275-80.
The in vivo antiplasmodial, analgesic and anti-inflammatory properties of Erythrina senegalensis, an ornamental plant commonly used in Northern Nigeria for the treatment of fevers, was evaluated. Aqueous extracts of the stem bark of the plant was used for the study. The in vivo antiplasmodial activity of the aqueous extract against Plasmodium berghei was assessed using the suppressive and curative test procedures. Analgesic activity was assessed using the acetic acid (0.75%v/v) induced abdominal constriction, while the anti-inflammatory activity was evaluated on egg-albumin induced paw oedema in rats as a model of acute inflammation. The stem bark extract of E. senegalensis exhibited only slight antiplasmodial activity while significant (P

14598212
Sairafianpour M, Bahreininejad B, Witt M, Ziegler HL, Jaroszewski JW, Staerk D
Terpenoids of Salvia hydrangea: two new, rearranged 20-norabietanes and the effect of oleanolic acid on erythrocyte membranes.
Planta Med. 2003 Sep;69(9):846-50.
Four abietane-type terpenoids, including two known royleanones and two new, rearranged 20-norabietanes, were isolated from the roots of the Iranian medicinal plant Salvia hydrangea DC. ex Bentham (Lamiaceae), which is used as an anthelmintic and antileishmanial remedy. Their structures were established using COSY, NOESY, HSQC, and HMBC spectral data. The possible identity of one of the 20-norabietanes with demethylmulticauline, previously reported from a different Salvia species, is discussed. A moderate in vitro antiplasmodial effect of the extract of S. hydrangea flowers was found to be associated with the presence of large amounts of pentacyclic triterpenes, mainly oleanolic acid. The observed antiplasmodial activity of oleanolic acid is apparently due to its incorporation into the erythrocyte membrane, which adversely affects

the growth of Plasmodium falciparum parasites. Thus, oleanolic acid caused transformation of erythrocytes into stomatocytes in the concentration range where the in vitro antiplasmodial activity was observed.

11720520
Sairafianpour M, Christensen J, Staerk D, Budnik BA, Kharazmi A, Bagherzadeh K, Jaroszewski JW
Leishmanicidal, antiplasmodial, and cytotoxic activity of novel diterpenoid 1,2-quinones from Perovskia abrotanoides: new source of tanshinones.
J Nat Prod. 2001 Nov;64(11):1398-403.
Cryptotanshinone (1), a quinoid diterpene with a nor-abietane skeleton, and three new natural products, 1beta-hydroxycryptotanshinone (2), 1-oxocryptotanshinone (3), and 1-oxomiltirone (4), were isolated from roots of the Iranian medicinal plant Perovskia abrotanoides. Their structures were established using homo- and heteronuclear two-dimensional NMR experiments, supported by HRMS. The total amount of tanshinones isolated from dry roots of Perovskia abrotanoides was about 1.5%. The compounds exhibited leishmanicidal activity in vitro (IC(50) values in the range 18-47 microM). These findings provide a rationale for traditional use of the roots in Iran as a constituent of poultices for treatment of cutaneous leishmaniasis. The isolated tanshinones also inhibited growth of cultured malaria parasites (3D7 strain of Plasmodium falciparum), drug-sensitive KB-3-1 human carcinoma cell line, multidrug-resistant KB-V1 cell line, and human lymphocytes activated with phytohaemagglutinin A (IC(50) values in the range 5-45 microM). The toxicity of tanshinones toward the drug-sensitive KB-3-1 and the multidrug-resistant KB-V1 cells was the same, indicating that the compounds are not substrates for the P-glycoprotein drug efflux pump.

12502308
Sairafianpour M, Kayser O, Christensen J, Asfa M, Witt M, Staerk D, Jaroszewski JW
Leishmanicidal and antiplasmodial activity of constituents of Smirnowia iranica.
J Nat Prod. 2002 Dec;65(12):1754-8.
Three unusual, highly oxygenated novel phenylpropanoids (1-3) and two novel isoflavans, 8-prenylmucronulatol (4) and smiranicin (6), were isolated from Smirnowia iranica together with a previously described isoflavan, glyasperin H (5). The structures were established using homo- and heteronuclear two-dimensional NMR experiments. The isoflavans significantly inhibited the growth of extracellular stages of three Leishmania species in vitro, their activity against the intracellular stages being considerably lower. 8-Prenylmucronulatol (4) showed moderate in vitro toxicity against Plasmodium falciparum, without noticeable erythrocyte membrane effects at the inhibitory concentration. Because of the structural relationship of isoflavans with chalcones and aurones, some of which are potent antiprotozoal agents, the isoflavan skeleton may be a template structure in search for new compounds with leishmanicidal and antiplasmodial activity.

12684889
Sanon S, Azas N, Gasquet M, Ollivier E, Mahiou V, Barro N, Cuzin-Ouattara N, Traore AS, Esposito F, Balansard G, Timon-David P
Antiplasmodial activity of alkaloid extracts from Pavetta crassipes (K. Schum) and Acanthospermum hispidum (DC), two plants used in traditional medicine in Burkina Faso.
Parasitol Res. 2003 Jul;90(4):314-7. Epub 2003 Apr 4.
In the course of the search for new antimalarial compounds, a study of plants traditionally used against malaria in Burkina Faso was made. An ethnobotanical study permitted the identification of plants currently used by the traditional healers and herbalists. Two plants among them were selected for further study: Pavetta crassipes (K. Schum) and Acanthospermum hispidum (DC). Alkaloid extracts of these plants were tested in vitro against two reference clones of Plasmodium falciparum: the W2 chloroquine-resistant and the D6 chloroquine-sensitive strains. Significant inhibitory activity was observed with Pavetta crassipes (IC(50)=1.23 microg/ml) and A. hispidum (IC(50)=5.02 microg/ml). Antiplasmodial activity was also evaluated against six Plasmodium falciparum isolates from children between 4 and 10 years old. The IC(50) values for the alkaloid extracts were in the range 25-670 ng/ml. These results indicated that P. falciparum wild strains were more sensitive to the alkaloid extracts than strains maintained in continuous culture. Moreover, the alkaloid extracts exhibit good in vitro antimalarial activity and weak cytotoxicity against three human cell lines (THP1, normal melanocytes, HTB-66). Isolation and structural determination are now necessary in order to precisely determine the active compounds.

12738078
Sanon S, Ollivier E, Azas N, Mahiou V, Gasquet M, Ouattara CT, Nebie I, Traore AS, Esposito F, Balansard G, Timon-David P, Fumoux F
Ethnobotanical survey and in vitro antiplasmodial activity of plants used in traditional medicine in Burkina Faso.
J Ethnopharmacol. 2003 Jun;86(2-3):143-7.

In Burkina Faso, most people in particular, in rural areas, use traditional medicine and medicinal plants to treat usual diseases. In the course of new antimalarial compounds, an ethnobotanical survey has been conducted in different regions. Seven plants, often cited by traditional practitioners and not chemically investigated, have been selected for an antiplasmodial screening: Pavetta crassipes (K. Schum), Acanthospermum hispidum (DC), Terminalia macroptera (Guill. et Perr), Cassia siamea (Lam), Ficus sycomorus (L), Fadogia agrestis (Schweinf. Ex Hiern) and Crossopteryx febrifuga (AFZ. Ex G. Don) Benth. Basic, chloroform, methanol, water-methanol and aqueous crude extracts have been prepared and tested on Plasmodium falciparum chloroquine-resistant W2 strain. A significant activity has been observed with alkaloid extract of P. crassipes (IC(50)<IC(50)

15549667
Sawadjoon S, Kittakoop P, Isaka M, Kirtikara K, Madla S, Thebtaranonth Y
Antiviral and antiplasmodial spirodihydrobenzofuran terpenes from the fungus Stachybotrys nephrospora.
Planta Med. 2004 Nov;70(11):1085-7.
Two known spirodihydrobenzofuran terpenes (1 and 2) were isolated from a mycelium extract of the fungus Stachybotrys nephrospora BCC 3900. Compound 1 (Mer-NF5003F or stachybotrydial) exhibited potent antiviral activity (the IC50 value of 4.32 microg/mL) comparable to the standard drug, acyclovir, while compound 2 was inactive against the HSV-1 virus. Both 1 and 2 possessed antiplasmodial activity (IC50 values of 0.85 and 0.15 microg/mL for 1 and 2, respectively), and were not toxic towards the Vero cell line. A regiospecific conversion of the dialdehyde 1 to the lactone 2 proceeded simply under acidic conditions.

10882627
Schlotmann T, Waase I, Julch C, Klauenberg U, Muller-Myhsok B, Dietrich M, Fleischer B, Broker BM
CD4 alphabeta T lymphocytes express high levels of the T lymphocyte antigen CTLA-4 (CD152) in acute malaria.
J Infect Dis. 2000 Jul;182(1):367-70. Epub 2000 Jun 30.
The role of T lymphocytes in human acute malaria remains under debate. The kinetics of T cell activation in acute malaria were investigated, with emphasis on CTLA-4 (CD152). In patients with malaria, CTLA-4 expression by CD4 alphabeta T lymphocytes was highly increased. After initiation of antiplasmodial treatment, it returned to control values within a few days. gammadelta T cells, which also are implicated in the pathogenesis of human malaria, did not express CTLA-4. The level of CTLA-4 expression at the time of hospital admission was correlated positively with other markers of disease severity-the peak of the parasitemia and the peak of serum neopterin levels. These results show that CTLA-4 is a sensitive and dynamic marker for T lymphocyte activation. Its strong increase in acute malaria argues for the involvement of T cells in the human immune response to plasmodia.

12521264
Schwikkard S, van Heerden FR
Antimalarial activity of plant metabolites.
Nat Prod Rep. 2002 Dec;19(6):675-92.
This review covers the structures of compounds with antiplasmodial activity isolated from plants and is organized according to plant family. A total of 170 structures has been reviewed from 186 references found in the literature up to December 2000.

15913846
Seebacher W, Brun R, Kaiser M, Saf R, Weis R
Synthesis and evaluation of the antitrypanosomal and antiplasmodial activities of new 4-aminobicyclo[2.2.2]octane derivatives.
Eur J Med Chem. 2005 Sep;40(9):888-96.
Several new 4-amino-6,7-diphenylbicyclo[2.2.2]octane derivatives, methylthiosemicarbazones of bicyclo[2.2.2]octan-2-ones and esters of bicyclo[2.2.2]octan-2-ols were prepared. Their antitrypanosomal activities against Trypanosoma brucei rhodesiense (STIB 900) and their antiplasmodial activity against the K1 strain of Plasmodium falciparum (resistant to chloroquine and pyrimethamine) were investigated using microplate assays. In addition to that, the cytotoxicity of the new compounds was determined using L-6 cells. The methylthiosemicarbazones show moderate antiprotozoal activities whereas some of the esters of piperonylic acid, homopiperonylic acid and 2-naphtoic acid exhibit remarkable antitrypanosomal and antiplasmodial activity.

15734294
Seebacher W, Schlapper C, Brun R, Kaiser M, Saf R, Weis R
Antiprotozoal activities of new bicyclo[2.2.2]octan-2-imines and esters of bicyclo[2.2.2]octan-2-ols.
Eur J Pharm Sci. 2005 Mar;24(4):281-9. Epub 2004 Dec 29.

Several bicyclo[2.2.2]octan-2-imines and esters of bicyclo[2.2.2]octan-2-ols were prepared. Their antitrypanosomal and antiplasmodial activities against Trypanosoma brucei rhodesiense (STIB 900) and the K1 strain of Plasmodium falciparum (resistant to chloroquine and pyrimethamine) were determined using microplate assays. Two of the synthesized bicyclo[2.2.2]octan-2-one 4'-phenylthiosemicarbazones showed the highest antitrypanosomal activity (IC(50)

11180515
Sharma P, Sharma JD
A review of plant species assessed in vitro for antiamoebic activity or both antiamoebic and antiplasmodial properties.
Phytother Res. 2001 Feb;15(1):1-17.
The resurgence of the protozoal diseases amoebiasis and malaria has been known to occur, from time to time, in endemic and epidemic proportions all over the world. Furthermore, the import of these individual pathogens to other areas from tropical regions encourages these protozoal diseases to occur on a global scale with considerable associated mortality and morbidity. From time immemorial, the cure of these diseases has been attempted with the use of traditional plant products, derived from such species as are available within local habitats and ecosystems, and dependent on their host community for their conservation. Scientific validation and in vitro investigation, continues to be an important requirement for drug development, particularly with the emergence of resistance and cross resistance to some standard drugs used in such protozoal diseases. This paper provides a comparative compilation of the various studies reported between 1982 and 1999, on plants with antiamoebic activities and those which possess both antiamoebic and antiplasmodial activities. The results suggest that it is advisable to increase efforts towards the conservation of such plants, in order to retain their economic and therapeutic significance.

11274824
Sharma P, Sharma JD
In vitro hemolysis of human erythrocytes -- by plant extracts with antiplasmodial activity.
J Ethnopharmacol. 2001 Mar 3;74(3):239-43.
Human erythrocytes were exposed in a dose dependent manner to various ethanolic plant extracts, and fractions obtained from plant parts of Calotropis procera (Ait.) R. Br. and the gum--oleo resin of Commiphora wightii (Arnott.) Bhand. These have been screened for in vitro schizontocidal activity and graded with respect to their 50% inhibitory concentration (IC(50)) derived from the twofold serial dilution of the dose range 0.0625--2 mg/ml. An attempt had been made to relate their antiplasmodial activity with their cytotoxicity as represented by the in vitro rate of hemolysis. Intact erythrocytes were found to respond with a dose--time-integral and fitted to models of pseudo first-order reaction, Michaelis--Menten equation and Hill equation with k(1), k(2) and k(3) as their rate constants, respectively. Hemolysis isotherms of flower and root of C. procera and gum--oleo resin of C. wightii extracts were representative. Erythrocytic membrane instability is possibly a major factor as has been earlier reported with ethanol and chloroquine for the cytotoxicity of these plant extracts.

11167038
Simonsen HT, Nordskjold JB, Smitt UW, Nyman U, Palpu P, Joshi P, Varughese G
In vitro screening of Indian medicinal plants for antiplasmodial activity.
J Ethnopharmacol. 2001 Feb;74(2):195-204.
Plants traditionally used in India to treat fever or malaria were examined in vitro for antiplasmodial properties against Plasmodium falciparum. Of 80 analysed ethanol extracts, from 47 species, significant effects were found for 31 of the extracts. These represent 23 different species from 20 families. Of the active species 20 were tested against P. falciparum for the first time. The following five species seems to be of special interest for further antimalarial studies, Casearia elliptica, Holarrhena pubescens, Pongamia pinnata, Soymida febrifuga, and Plumbago zeylanica.

16392829
Skytte DM, Nielsen SF, Chen M, Zhai L, Olsen CE, Christensen SB
Antimalarial and antiplasmodial activities of norneolignans. Syntheses and SAR.
J Med Chem. 2006 Jan 12;49(1):436-40.
A systematic change of the substituents and side chain of the norneolignan hinokiresinol afforded a 10 fold improvement of the IC(50) value toward inhibition of the growth of Plasmodium falciparum. The more potent compounds controlled the parasitemia in mice infected with Plasmodium berghei.

10389648
Smeijsters LJ, Franssen FF, Naesens L, de Vries E, Holy A, Balzarini J, de Clercq E, Overdulve JP
Inhibition of the in vitro growth of Plasmodium falciparum by acyclic nucleoside phosphonates.
Int J Antimicrob Agents. 1999 Jun;12(1):53-61.

Forty-eight acyclic nucleoside phosphonates (putative prodrugs of acyclic nucleoside triphosphate inhibitors of DNA replication) have been evaluated for in vitro antiplasmodial activity. Only certain purine derivatives with a hydroxyl group attached to the acyclic sugar moiety displayed antiplasmodial activity. The two most active analogs were (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine ((S)-HPMPA, IC50=0.18+/-0.07 microM) and (S)-3-deaza-HPMPA (IC50=0.29+/-0.08 microM). Their cyclic derivatives, containing an ester bond between the phosphonate and the hydroxyl group, were slightly less active. All tested compounds that lacked the hydroxyl group, including potent antiretrovirus analogs such as 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and the (S)-HPMPA derivatives (R)-PMPA and (S)-FPMPA, did not show any activity, even at very high concentrations (>250 microM). Similarly, pyrimidine analogs of (S)-HPMPA, such as (S)-HPMPT, (S)-HPMPU and the anti-herpesvirus analog (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine ((S)-HPMPC), were devoid of any antiplasmodial activity. In addition, 11 acyclic nucleoside (non-phosphorylated) analogs--which in contrast to the acyclic nucleoside phosphonates require the presence of a monophosphorylating enzyme for the first activation step--were tested. None of them inhibited the growth of the parasite. In short three chemical entities seem to be imperative for antiplasmodial activity: a purine base, a hydroxyl group in the acyclic side chain and a phosphonate group terminating this chain.

10985079
Staerk D, Lemmich E, Christensen J, Kharazmi A, Olsen CE, Jaroszewski JW
Leishmanicidal, antiplasmodial and cytotoxic activity of indole alkaloids from Corynanthe pachyceras.
Planta Med. 2000 Aug;66(6):531-6.
Five indole alkaloids, corynantheidine, corynantheine, dihydrocorynantheine, alpha-yohimbine and corynanthine were isolated from bark of Corynanthe pachyceras K. Schum. (Rubiaceae). The structures were established by spectroscopic methods, including previously unreported assignment of all 1H-NMR resonances by COSY and NOESY experiments. These and related alkaloids showed pronounced activity against Leishmania major promastigotes (IC50 at the micromolar level) but no significant in vitro antiplasmodial activity (against chloroquine-sensitive Plasmodium falciparum). Cytotoxicity assessed with drug sensitive KB-3-1 and multidrug-resistant KB-V1 cell lines was low; the alkaloids are apparently not substrates for the P-glycoprotein (P-170) efflux pump.

12096003
Steele JC, Phelps RJ, Simmonds MS, Warhurst DC, Meyer DJ
Two novel assays for the detection of haemin-binding properties of antimalarials evaluated with compounds isolated from medicinal plants.
J Antimicrob Chemother. 2002 Jul;50(1):25-31.
Forty-two compounds isolated from nine plants used within South America for the treatment of malaria were tested for haemin binding using two novel, rapid screening methods. The data obtained were analysed with respect to IC(50) values for in vitro toxicity to Plasmodium falciparum trophozoites. One method, a multiwell assay based on the inhibition of the interaction of haemin with glutathione (GSH), is sensitive in the 10 microM range, takes c. 1 h and is suitable for either a high throughput screen or rapid assay during natural product isolation. Of 19 compounds showing antiplasmodial activity (IC(50) < 40 microM), 16 (84%) showed >40% inhibition of GSH-haemin reaction. The sensitivity and specificity of the assay were 0.85 and 0.82, respectively. The positive predictive value was 0.81 and the negative predictive value 0.86. A more sensitive assay (0.1 microM range) is based on the reversal by haemin-binding compounds of the haemin inhibition of the L-dopachrome-methyl ester tautomerase activity of human macrophage migration inhibitory factor. This assay gives a better idea of the affinity of interaction and uses very small amounts of test compound. The log[RI(50)] of eight of the compounds that tested positive in the above assays together with those of quinine and chloroquine showed a positive correlation with log[antiplasmodial IC(50)] for strain T9-96 (r = 0.824) and strain K1 (r = 0.904). Several of the antimalarial compounds that bind haemin are isoquinolines, a class not shown previously to interact with haemin.

11809075
Steele JC, Veitch NC, Kite GC, Simmonds MS, Warhurst DC
Indole and beta-carboline alkaloids from Geissospermum sericeum.
J Nat Prod. 2002 Jan;65(1):85-8.
The indole alkaloid geissoschizoline (1) and two new derivatives, geissoschizoline N(4)-oxide (2) and 1,2-dehydrogeissoschizoline (3), were obtained from the bark of Geissospermum sericeum together with the beta-carboline alkaloid flavopereirine (4). The in vitro antiplasmodial activity of these compounds was evaluated in chloroquine-resistant (K1) and chloroquine-sensitive (T9-96) Plasmodium falciparum. Their cytotoxicity was determined in a human (KB) cell line.

10190183
Steele JC, Warhurst DC, Kirby GC, Simmonds MS

In vitro and in vivo evaluation of betulinic acid as an antimalarial.
Phytother Res. 1999 Mar;13(2):115-9.
The lupane-type triterpene betulinic acid was isolated from an ethanol extract of the root bark of the Tanzanian tree Uapaca nitida Mull-Arg. (Euphorbiaceae). The in vitro antiplasmodial IC50 values of betulinic acid against chloroquine resistant (K1) and sensitive (T9-96) Plasmodium falciparum were found to be 19.6 micrograms/mL and 25.9 micrograms/mL, respectively. The in vitro activities of several related triterpenes were also evaluated. Betulin was found to be inactive at 500 micrograms/mL for both K1 and T9-96. Ursolic acid exhibited IC50 values of 36.5 micrograms/mL and 28 micrograms/mL, and oleanolic acid exhibited IC50 values of 88.8 micrograms/mL and 70.6 micrograms/mL against K1 and T9-96, respectively. When betulinic acid was tested for in vivo activity in a murine malaria model (P. berghei) the top dosage employed of 250 mg/kg/day was ineffective at reducing parasitaemia and exhibited some toxicity. Betulinic acid has not previously been evaluated for in vivo activity. This is believed to be the first compound to be isolated from U. nitida.

16204994
Suksamrarn A, Buaprom M, Udtip S, Nuntawong N, Haritakun R, Kanokmedhakul S
Antimycobacterial and antiplasmodial unsaturated carboxylic acid from the twigs of Scleropyrum wallichianum.
Chem Pharm Bull (Tokyo). 2005 Oct;53(10):1327-9.
From the twigs of Scleropyrum wallichianum, a new unsaturated carboxylic acid, scleropyric acid (1), two new esters, beta-sitosteryl-3-O-scleropyrate (2) and stigmasteryl-3-O-scleropyrate (3), and two well-known sterols, beta-sitosterol (4) and stigmasterol (5), were isolated and characterized using spectroscopic methods. Compound 1 exhibited antimycobacterial activity with an MIC value of 25 microg/ml and showed antiplasmodial activity with an IC50 value of 7.2 microg/ml. Compounds 2 and 3 were inactive in both assays.

12963155
Suksamrarn A, Tanachatchairatana T, Kanokmedhakul S
Antiplasmodial triterpenes from twigs of Gardenia saxatilis.
J Ethnopharmacol. 2003 Oct;88(2-3):275-7.
Ten triterpenes (1-10) were isolated and identified from the twigs of Gardenia saxatilis (Rubiaceae) and were subjected to antiplasmodial evaluation against the parasite Plasmodium falciparum. The first six compounds, lupenone (1), lupeol (2), betulinic acid (3), oleanolic acid (4), ursolic acid (5), and winchic acid (27-O-feruloyloxybetulinic acid) (6) were inactive in the assay. The other four compounds, messagenic acid A (7) and messagenic acid B (8), the 27-O-p-(Z)- and 27-O-p-(E)-coumarate esters of betulinic acid, and a mixture of uncarinic acid E (27-O-p-(E)-coumaroyloxyoleanolic acid) (9) and 27-O-p-(E)-coumaroyloxyursolic acid (10) exhibited antiplasmodial activity, with the IC50 values of 1.5, 3.8 and 2.9 microg/ml, respectively. The results indicated that the p-coumarate moieties at the 27-position, both the cis and trans isomers, contributed to antiplasmodial activity. Introduction of a methoxyl group to the 3-position of the p-coumarate moiety to give a ferulate moiety resulted in loss of activity.

15930777
Takasu K, Shimogama T, Saiin C, Kim HS, Wataya Y, Brun R, Ihara M
Synthesis and evaluation of beta-carbolinium cations as new antimalarial agents based on pi-delocalized lipophilic cation (DLC) hypothesis.
Chem Pharm Bull (Tokyo). 2005 Jun;53(6):653-61.
Several beta-carbolines including naturally occurring substances and their corresponding cationic derivatives were synthesized and evaluated for antimalarial (antiplasmodial) activity in vitro and in vivo. A tetracyclic carbolinium salt was elucidated for antileishmanial and antitrypanosomal activities in vitro as well as antiplasmodial activity. Quarternary carbolinium cations showed much higher potencies in vitro than electronically neutral beta-carbolines and a good correlation was observed between pi-delocalized lipophilic cationic (DLC) structure and antimalarial efficacy. beta-Carbolinium compounds exhibit medium suppressive activity in vivo against rodent malaria.

15763374
Tamez PA, Lantvit D, Lim E, Pezzuto JM
Chemosensitizing action of cepharanthine against drug-resistant human malaria, Plasmodium falciparum.
J Ethnopharmacol. 2005 Apr 8;98(1-2):137-42.
We have established a system of in vitro and in vivo assays to prioritize plant extracts that can serve as a source of drug candidates for the treatment of malaria, an infectious disease that affects nearly 40% of the world's population. In the present study, we have investigated the biological potential of one such plant-derived drug lead, cepharanthine. In vitro growth inhibition studies indicated this compound possessed good antiplasmodial activity without mediating a cytotoxic response. Based on this selectivity, evaluations were

performed with an in vivo mouse model. Moderate activity was observed, inhibiting parasite growth by 46% at a dose of 100 mg/kg body weight (BW). We further assessed the ability of cepharanthine to serve as a drug in combination with a standard antimalarial regimen. Like chloroquine, cepharanthine inhibited the trophozoite stage of parasite growth. Isobolographic analyses revealed synergism with chloroquine, but only with the drug-resistant malaria clone, and single-dose drug-interaction studies demonstrated that cepharanthine lowered the half-maximal inhibitory concentration of chloroquine from 148.5 to 37.8 nM. In summary, since activity in the mouse model was only moderate, cepharanthine may be of greater value as a modulator of resistance, capable of prolonging the clinical utility of chloroquine.

15852483
Tasdemir D, Brun R, Perozzo R, Donmez AA
Evaluation of antiprotozoal and plasmodial enoyl-ACP reductase inhibition potential of turkish medicinal plants.
Phytother Res. 2005 Feb;19(2):162-6.
A total of 58 extracts of different polarity were prepared from various organs of 16 species of Turkish plants and screened for their antitrypanosomal, antileishmanial and antiplasmodial activities. No significant activity was observed against Trypanosoma cruzi, whereas many extracts showed appreciable trypanocidal potential against T. brucei rhodesiense, with the CHCl(3)-soluble portion of Phlomis kurdica being the most active (IC(50) 2.7 microg[sol]mL). Almost all extracts, particularly the CHCl(3) phases, exhibited growth inhibition activity against Leishmania donovani amastigotes. The CHCl(3)-solubles of Putoria calabrica roots (IC(50) 1.9 microg[sol]mL), Wendlandia ligustroides leaves (IC(50) 2.1 microg[sol]mL) and Rhododendron luteum leaves (IC(50) 2.3 microg[sol]mL) displayed the highest leishmanicidal potential. The majority of the extracts also possessed antiplasmodial activity against the multi-drug resistant K1 Plasmodium falciparum strain. The most potent antiplasmodial activity was observed with the CHCl(3) extracts of Phlomis kurdica (IC(50) 1.5 microg[sol]mL), P. leucophracta (IC(50) 1.6 microg[sol]mL), Scrophularia cryptophila (IC(50) 1.8 microg[sol]mL), Morina persica (IC(50) 1.9 microg[sol]mL) and the aqueous root extract of Asperula nitida subsp. subcapitellata (IC(50) 1.6 microg[sol]mL). Twenty-one extracts with significant antimalarial activity (IC(50) < 5 microg[sol]mL) were also tested for their ability to inhibit the purified enoyl-ACP reductase (FabI), a crucial enzyme in the fatty acid biosynthesis of P. falciparum. The CHCl(3) extract of Rhododendron ungernii leaves (IC(50) 10 microg[sol]mL) and the H(2)O-soluble portion of Rhododendron smirnovii leaves (IC(50) 0.4 microg[sol]mL) strongly inhibited the FabI enzyme. The preliminary data indicate that some (poly)phenolic compounds are responsible for the FabI inhibition potential of these extracts. The presented work reports for the first time the antiprotozoal activity of nine different genera as well as a target specific antimalarial screening for the identification of P. falciparum FabI inhibitors from medicinal plant extracts.

15182900
Tona L, Cimanga RK, Mesia K, Musuamba CT, De Bruyne T, Apers S, Hernans N, Van Miert S, Pieters L, Totte J, Vlietinck AJ
In vitro antiplasmodial activity of extracts and fractions from seven medicinal plants used in the Democratic Republic of Congo.
J Ethnopharmacol. 2004 Jul;93(1):27-32.
The in vitro antiplasmodial activity of seven EtOH extracts and twenty fractions from the partition of the initial ethanolic extracts from seven African medicinal plants used in the Democratic Republic of Congo (DR Congo) for the treatment of malaria was evaluated. The most active EtOH extracts (IC50 < 3 microg/ml) were those from Cassia occidentalis leaves, Euphorbia hirta whole plant, Garcinia kola stem bark and Phyllanthus niruri whole plant. Their respective petroleum ether soluble fractions also exhibited an antiplasmodial activity with IC50 < 3 microg/ml. EtOH extracts from Vernonia amygdalina leaves (5 < IC50 < 10 microg/ml), Tetracera poggei leaves (10 < IC50 < 50 microg/ml) and Morinda morindoides leaves (50 < IC50 < 100 microg/ml) were less active, but their petroleum ether fractions exhibited a pronounced antiplasmodial activity (IC50 < 3 microg/ml). The same observation could also be made for the petroleum ether fraction from Cassia occidentalis, Euphorbia hirta, Garcinia kola and Phyllanthus niruri. Isoamyl alcohol fractions from Euphorbia hirta, Phyllanthus niruri and Vernonia amygdalina showed IC50) values less than 3 microg/ml, and from Cassia occidentalis, Garcinia kola, Morinda morindoides and Tetracera poggei between 10 and 50 microg/ml. The observed antiplasmodial activity may be related to the presence of terpenes, steroids, coumarins, flavonoids, phenolic acids, lignans, xanthones and anthraquinones.

12738095
Tran QL, Tezuka Y, Ueda JY, Nguyen NT, Maruyama Y, Begum K, Kim HS, Wataya Y, Tran QK, Kadota S
In vitro antiplasmodial activity of antimalarial medicinal plants used in Vietnamese traditional medicine.
J Ethnopharmacol. 2003 Jun;86(2-3):249-52.
Among 42 extracts, prepared from 14 medicinal plants used in Vietnamese traditional medicine to treat malaria, 24 were found to have antiplasmodial activity by inhibiting the growth of the chloroquine-resistant

Plasmodium falciparum strain FCR-3 with EC(50) values less than 10 microg/ml. Each medicinal plant possessed at least one active extract. The methanol extract of Coscinium fenestratum had the strongest antiplasmodial activity with EC(50) value of 0.5 microg/ml. Activity-guided fractionation led to identification of berberine as the major active constituent.

10865459
Traore F, Faure R, Ollivier E, Gasquet M, Azas N, Debrauwer L, Keita A, Timon-David P, Balansard G
Structure and antiprotozoal activity of triterpenoid saponins from Glinus oppositifolius.
Planta Med. 2000 May;66(4):368-71.
Two new triterpenoid saponins, glinosides A and B, isolated from the aerial parts of Glinus oppositifolius, have been characterized by 1D, 2D, NMR and high-resolution mass spectral (HRMS) techniques. Their structures were established respectively as 16-O-(beta-arabinopyranosyl)-3-oxo-12,16 beta,21 beta,22-tetrahydroxyhopane for glinoside A and 16-O-(beta-arabinopyranosyl)-3-oxo-12,16 beta,22-trihydroxyhopane for glinoside B. Results presented evidence that fractions had a better antiplasmodial activity (IC50 = 31.80 micrograms/ml) than pure glinoside A (IC50 = 42.30 micrograms/ml).

11891084
Tshibangu JN, Chifundera K, Kaminsky R, Wright AD, Konig GM
Screening of African medicinal plants for antimicrobial and enzyme inhibitory activity.
J Ethnopharmacol. 2002 Apr;80(1):25-35.
Seven plant species, belonging to different families, were collected in the eastern part of the Republic of Congo (Kivu) based on ethnopharmacological information. Their dichloromethane and methanolic extracts were tested for biological activity. Five of the seven collected plants exhibited antiplasmodial activity with IC(50) values ranging from 1.1 to 9.8 microg/ml. The methanolic extract of Cissampelos mucronata was the most active one showing activity against chloroquine sensitive (D6) and chloroquine resistant (W2) Plasmodium falciparum strains with IC(50) values of 1.5 and 1.1 microg/ml, respectively. Additionally, this extract significantly inhibited the enzyme tyrosine kinase p56(lck) (TK). The dichloromethane extract of Amorphophallus bequaertii inhibited the growth of Mycobacterium tuberculosis with a MIC of 100 microg/ml and the methanolic extract of Rubus rigidus inhibited the activity of both enzymes HIV1-reverse transcriptase (HIV1-RT) and TK p56(lck).

16462055
Tuntiwachwuttikul P, Phansa P, Pootaeng-On Y, Taylor WC
Chemical constituents of the roots of Piper sarmentosum.
Chem Pharm Bull (Tokyo). 2006 Feb;54(2):149-51.
Sixteen compounds were isolated from the fresh roots of Piper sarmentosum. Seven of these have been previously isolated from the fruits and leaves of this plant: the aromatic alkene (1), 1-allyl-2-methoxy-4,5-methylenedioxybenzene (4), beta-sitosterol, pyrrole amide (6), sarmentine (10), sarmentosine (13) and pellitorine (14). (+)-Sesamin (2), horsfieldin (3), two pyrrolidine amides 11 and 12, guineensine (15) and brachystamide B (16) are new for P. sarmentosum. Sarmentamide A, B, and C (7-9) are new natural products. Compounds 1--4 and 6--16 were tested for antiplasmodial, antimycobacterial and antifungal activities.

16394547
Tuntiwachwuttikul P, Phansa P, Pootaeng-On Y, Taylor WC
Chromones from the branches of Harrisonia perforata.
Chem Pharm Bull (Tokyo). 2006 Jan;54(1):44-7.
Four new chromones, perforamone A, B, C, and D have been isolated together with six known compounds, peucenin-7-methyl ether, O-methylalloptaeroxylin, perforatic acid, eugenin, saikochromone A and greveichromenol, from the branches of Harrisonia perforata (Simaroubaceae). The structures were identified by spectroscopic data. The compounds were tested for antimycobacterial and antiplasmodial activities.

15921407
Van Miert S, Hostyn S, Maes BU, Cimanga K, Brun R, Kaiser M, Matyus P, Dommisse R, Lemiere G, Vlietinck A, Pieters L
Isoneocryptolepine, a synthetic indoloquinoline alkaloid, as an antiplasmodial lead compound.
J Nat Prod. 2005 May;68(5):674-7.
The antiprotozoal activities of three naturally occurring isomeric indoloquinoline alkaloids, i.e., cryptolepine (1), neocryptolepine (2), and isocryptolepine (3), and two dimeric indoloquinoline alkaloids, cryptoquindoline (6) and biscryptolepine (7), originally obtained from the plant Cryptolepis sanguinolenta, were compared with those of a new synthetic indoloquinoline isomer, isoneocryptolepine (4), and a quaternary derivative, N-methyl-isocryptolepinium iodide (5). The latter compounds showed a high antiplasmodial activity against the chloroquine-resistant Plasmodium falciparum strain K1 (IC50 of 0.23 +/- 0.04 and 0.017 +/- 0.004 microM,

respectively), while the cytotoxicity (L6 cells) was 4.32 +/- 0.04 and 12.7 +/- 2.0 microM, respectively. Isoneocryptolepine (4) was found to act as an inhibitor of beta-hematin formation and as a DNA-intercalating agent.

15582513
Van Miert S, Jonckers T, Cimanga K, Maes L, Maes B, Lemiere G, Dommisse R, Vlietinck A, Pieters L
In vitro inhibition of beta-haematin formation, DNA interactions, antiplasmodial activity, and cytotoxicity of synthetic neocryptolepine derivatives.
Exp Parasitol. 2004 Nov-Dec;108(3-4):163-8.
Neocryptolepine, a minor alkaloid of Cryptolepis sanguinolenta, was investigated as a lead for new antiplasmodial agents, because of its lower cytotoxicity than cryptolepine, the major alkaloid. Synthetic 2- or 3-substituted neocryptolepine derivatives were evaluated for their biological activity. In addition to the antiplasmodial activity (Plasmodium falciparum chloroquine-sensitive and -resistant) also the cytotoxicity (MRC-5 cells) was determined. Several compounds such as 2-bromoneocryptolepine showing higher and more selective antiplasmodial activity than neocryptolepine were obtained. Several functional assays and in vitro tests were used to obtain additional information on the mechanism of action, i.e., the beta-haematin formation inhibitory assay (detoxification of haem) and the DNA-methylgreen displacement assay (interaction with DNA). It could be demonstrated that the 2- or 3-substituted neocryptolepine derivatives investigated here have about the same potency to inhibit the beta-haematin formation as chloroquine, indicating that inhibition of haemozoin formation makes at least an important contribution to their antiplasmodial activity, although their in vitro antiplasmodial activity is still less than chloroquine.

11374952
Verotta L, Dell'Agli M, Giolito A, Guerrini M, Cabalion P, Bosisio E
In vitro antiplasmodial activity of extracts of Tristaniopsis species and identification of the active constituents: ellagic acid and 3,4,5-trimethoxyphenyl-(6'-O-galloyl)-O-beta-D-glucopyranoside.
J Nat Prod. 2001 May;64(5):603-7.
Screening of plants from New Caledonia for antiplasmodial activity against Plasmodium falciparum revealed that methanolic extracts of the leaves and bark of Tristaniopsis calobuxus, T. yateensis, and T.glauca inhibited the growth of chloroquine-sensitive and -resistant clones. Ellagic acid and the new compound 3,4,5-trimethoxyphenyl-(6'-O-galloyl)-O-beta-D-glucopyranoside were identified as the active constituents (IC50 0.5 and 3.2 microM, respectively). The growth inhibition of both clones was comparable. The compounds showed negligible or very low cytotoxicity to human skin fibroblasts and Hep G2 cells when tested at concentrations ranging from 0.5 to 100 microM.

15729632
Vongvanich N, Kittakoop P, Charoenchai P, Intamas S, Danwisetkanjana K, Thebtaranonth Y
Combretastatins D-3 and D-4, new macrocyclic lactones from Getonia floribunda.
Planta Med. 2005 Feb;71(2):191-3.
Chemical investigation of biologically active compounds of Getonia floribunda led to the isolation of two new macrocyclic lactones, combretastatins D-3 (1) and D-4 (2). The structures of these compounds were confirmed by spectroscopic analyses. Combretastatin D-3 (1) exhibited cytotoxicity towards the small-cell lung cancer cell line (NCI-H187, IC50=13.0 +/- 0.2 microg/mL) but was inactive against KB, BC-1, and Vero cell lines. Combretastatin D-3 (1) showed weak antitubercular activity with a minimum inhibitory concentration (MIC) of 100.0 microg/mL, and was inactive towards the malarial parasite. Combretastatin D-4 (2) was inactive in all antitubercular, antiplasmodial, and cytotoxic assays.

12860312
Vonthron-Senecheau C, Weniger B, Ouattara M, Bi FT, Kamenan A, Lobstein A, Brun R, Anton R
In vitro antiplasmodial activity and cytotoxicity of ethnobotanically selected Ivorian plants.
J Ethnopharmacol. 2003 Aug;87(2-3):221-5.
Eight extracts from four Ivorian medicinal plants, traditionally used to treat malaria, were tested for their antiplasmodial activity in vitro by assessing their ability to inhibit the uptake of [3H]hypoxanthine into the Plasmodium falciparum K1 chloroquine-resistant strain. The most active extract was the methylene chloride extract of Anogeissus leiocarpus which exhibited an IC(50) value of 3.8 micro g/ml. Inhibition of the growth of Plasmodium falciparum was also observed with the methylene chloride extract of Cochlospermum planchonii and Microdesmis keayana as well as with both methylene chloride and methanolic extracts of Hymenocardia acida.

15848033
Waako PJ, Gumede B, Smith P, Folb PI
The in vitro and in vivo antimalarial activity of Cardiospermum halicacabum L. and Momordica foetida Schumch. Et Thonn.

J Ethnopharmacol. 2005 May 13;99(1):137-43.
Two plants Cardiospermum halicacabum L. and Momordica foetida Schumch. Et Thonn traditionally used to treat symptoms of malaria in parts of East and Central Africa were screened for in vitro and in vivo antimalarial activity. Using the nitro tetrazolium blue-based parasite lactate dehydrogenase assay as used by [Makler, M.T., Ries, J.M., Williams, J.A., Bancroft, J.E., Piper, R.C., Gibbins, B.L., Hinrichs, D.J., 1993. Parasite lactate dehydrogenase as an assay for Plasmodium falciparum drug sensitivity. American Journal of Tropical Medicine and Hygiene 48, 739-741], water extracts from the two plants were found to have weak in vitro antiplasmodial activity with 50% inhibitory concentrations (IC50s) greater than 28.00 microg/ml. In vivo studies of water extracts from the two plants showed that Momordica foetida given orally in the dose range 10, 100, 200 and 500 mg/kg twice daily prolonged survival of Plasmodium berghei (Anka) infected mice from 7.0+/-1.8 to 17.9+/-1.8 days. The water extract of Cardiospermum halicacabum L was toxic to mice, none surviving beyond day 4 of oral administration, with no evidence of protection against Plasmodium berghei malaria. The study emphasizes the discrepancy that might be found between in vitro and in vivo testing of plant-derived antimalarial extracts and the need to consider in vitro antiplasmodial data with this in mind. Further studies on Momordica foetida as a source of an antimalarial remedy are indicated on the basis of these results.

14698520
Wanyoike GN, Chhabra SC, Lang'at-Thoruwa CC, Omar SA
Brine shrimp toxicity and antiplasmodial activity of five Kenyan medicinal plants.
J Ethnopharmacol. 2004 Jan;90(1):129-33.
The organic extracts of leaves and roots of five plants used for treating malaria in Central, Nairobi and Rift Valley Provinces, Kenya were tested for brine shrimp lethality and in vitro antiplasmodial activity against chloroquine sensitive and resistant strains of Plasmodium falciparum. Of the plants tested, 60% were toxic to the brine shrimp (LC(50)

14505493
Warhurst DC, Craig JC, Adagu IS, Meyer DJ, Lee SY
The relationship of physico-chemical properties and structure to the differential antiplasmodial activity of the cinchona alkaloids.
Malar J. 2003 Sep 1;2:26. Epub 2003 Sep 1.
BACKGROUND: The 8-amino and 9-hydroxy substituents of antimalarial cinchona alkaloids have the erythro orientation while their inactive 9-epimers are threo. From the X-ray structures a 90 degrees difference in torsion angle between the N1-H1 and C9-O12 bonds in the two series is believed to be important. In order to kill the malaria parasite, alkaloids must cross the erythrocyte and parasite membranes to accumulate in the acid digestive vacuole where they prevent detoxication of haematin produced during haemoglobin breakdown. METHODS: Ionization constants, octanol/water distribution and haematin interaction are examined for eight alkaloids to explain the influence of small structural differences on activity. RESULTS: Erythro isomers have a high distribution ratio of 55:1 from plasma to the erythrocyte membrane, while for the more basic threo epimers this is only 4.5:1. This gives an increased transfer rate of the erythro drugs into the erythrocyte and thence into the parasite vacuole where their favourable conformation allows interaction with haematin, inhibiting its dimerization strongly (90 +/- 7%) and thereby killing the parasite. The threo compounds not only enter more slowly but are then severely restricted from binding to haematin by the gauche alignment of their N1-H1 and C9-O12 bonds. Confirmatory molecular models allowed measurement of angles and bond lengths and computation of the electronic spectrum of a quinine-haematin complex. CONCLUSION: Differences in the antiplasmodial activity of the erythro and threo cinchona alkaloids may therefore be attributed to the cumulative effects of lipid/aqueous distribution ratio and drug-haematin interaction. Possible insights into the mechanism of chloroquine-resistance are discussed.

15013193
Weniger B, Lagnika L, Vonthron-Senecheau C, Adjobimey T, Gbenou J, Moudachirou M, Brun R, Anton R, Sanni A
Evaluation of ethnobotanically selected Benin medicinal plants for their in vitro antiplasmodial activity.
J Ethnopharmacol. 2004 Feb;90(2-3):279-84.
Twenty extracts from nine Benin medicinal plants, traditionally used to treat malaria, were screened for in vitro antiplasmodial activity towards Plasmodium falciparum K1 chloroquine resistant and 3D7 chloroquine sensitive strains. All plants showed antiplasmodial activity below 10 microg/ml. Nine extracts exhibited IC50 values below 5 microg/ml towards one or both of the two strains. The most active extract towards the sensitive 3D7 strain was the methanolic extract of Croton lobatus aerial part, with an IC50 value of 0.38 microg/ml. The best inhibition of the growth of Plasmodium falciparum resistant K1 strain was observed with the methylene chloride extract of Hybanthus enneaspermus and with the methanolic extract of Croton lobatus roots (IC50=2.57 and 2.80 microg/ml, respectively).

16428025
Weniger B, Vonthron-Senecheau C, Kaiser M, Brun R, Anton R
Comparative antiplasmodial, leishmanicidal and antitrypanosomal activities of several biflavonoids.
Phytomedicine. 2006 Feb;13(3):176-80. Epub 2005 Jun 28.
The antiplasmodial, leishmanicidal and antitrypanosomal activities of eight natural biflavonoids were estimated in vitro on a chloroquine-resistant strain of Plasmodium falciparum, axenically grown Leishmania donovani amastigotes and Trypanosoma cruzi trypomastigotes and Trypanosoma brucei rhodesiense bloodstream forms. Lanaroflavone showed the highest antiplasmodial activity (IC(50) = 0.48 microM), isoginkgetin was the most active leishmanicidal compound (IC(50) = 1.9 microM), whereas ginkgetin (IC(50) = 11 microM) and isoginkgetin (IC(50) = 13 microM) showed the best antitrypanosomal activity in our assays. The cytotoxicity and the selectivity indices for the most active compounds were also estimated. Lanaroflavone exhibited a high selectivity index value (SI = 159), indicating selective antiplasmodial activity.

12547260
Wright AD
GC-MS and NMR analysis of Phyllidiella pustulosa and one of its dietary sources, the sponge Phakellia carduus.
Comp Biochem Physiol A Mol Integr Physiol. 2003 Feb;134(2):307-13.
Gas-chromatographic and mass-spectrometric and NMR analyses of the lipophilic extract of the nudibranch Phyllidiella pustulosa and the sponge Phakellia carduus clearly showed that the sponge formed a major part of the nudibranchs diet. The analyses also indicated that the nudibranch accumulates some of the sponge metabolites in preference to others. The main components of the extracts were identified as the new natural product 10-isothiocyano-4-cadinene (1), axisonitrile-3 (2), and a number of other sesquiterpenes similar to 1 and 2. Also positively identified, in the extract of the sponge were the two sterols (3beta,22E)-ergosta-5,8,22-trien-3-ol (4) and (3beta,22E)-stigmasta-5,7,22-trien-3-ol (5), and in the nudibranch extract caryophyllene (3). The new natural product 10-isothiocyano-4-cadinene (1) was shown to have moderate antiplasmodial activity (IC(50) 1.5 microgram/ml towards Plasmodium falciparum clones K1, and NF54).

12086492
Wright AD, Goclik E, Konig GM, Kaminsky R
Lepadins D-F: antiplasmodial and antitrypanosomal decahydroquinoline derivatives from the tropical marine tunicate Didemnum sp.
J Med Chem. 2002 Jul 4;45(14):3067-72.
From a new tunicate species, belonging to the genus Didemnum, three alkaloids possessing an unusual and extremely rare decahydroquinoline skeleton and showing significant and selective antiplasmodial and antitrypanosomal activity were obtained as follows: (2R*,3S*,4aR*,5R*,8aS*)-decahydro-3-hydroxy-5-(5'-hydroxyoctyl)-2-methylqu inoline (lepadin D,1), its quaternary nitrogen derivative (2), (2R*,2"E,3S*,4aR*,5R*,8aS*)-decahydro-3-hydroxy-5-(5'-hydroxyoctyl)-2-meth yl-3-quinolinyl ester 2"-octenoic acid (lepadin E, 3), and (2S*,2"E,3S*,4aR*,5R*,8aS*)-decahydro-3-hydroxy-5-(5'-hydroxyoctyl)-2-meth yl-3-quinolinyl ester 2"-octenoic acid (lepadin F, 4). These isolates may well serve as lead structures for the development of new antimalarial drugs.

16254832
Wright AD, Lang-Unnasch N
Potential antimalarial lead structures from fungi of marine origin.
Planta Med. 2005 Oct;71(10):964-6.
Antiplasmodial and cytotoxicity testing of five highly oxygenated natural products (6R,12R,14R-colletoketol, 6R,11R,12R,14R-colletoketodiol, dihydrobotrydial, pycnidione, and 3R,4S-hydroxymellein), all derived from fungi of marine origin, showed one of them, pycnidione, to have activities against three different strains of Plasmodium falciparum in the sub-micromolar (microM) range. Although the mean selectivity index of 1 for the observed antiplasmodial activity of 4 is low, pycnidione's usefulness as a potential lead structure should not be ignored.

11300869
Wright AD, Wang H, Gurrath M, Konig GM, Kocak G, Neumann G, Loria P, Foley M, Tilley L
Inhibition of heme detoxification processes underlies the antimalarial activity of terpene isonitrile compounds from marine sponges.
J Med Chem. 2001 Mar 15;44(6):873-85.
A series of terpene isonitriles, isolated from marine sponges, have previously been shown to exhibit antimalarial activities. Molecular modeling studies employing 3D-QSAR with receptor modeling methodologies performed with these isonitriles showed that the modeled molecules could be used to generate a pharmacophore hypothesis consistent with the experimentally derived biological activities. It was also shown that one of the modeled compounds, diisocyanoadociane (4), as well as axisonitrile-3 (2), both of

which have potent antimalarial activity, interacts with heme (FP) by forming a coordination complex with the FP iron. Furthermore, these compounds were shown to inhibit sequestration of FP into beta-hematin and to prevent both the peroxidative and glutathione-mediated destruction of FP under conditions designed to mimic the environment within the malaria parasite. By contrast, two of the modeled diterpene isonitriles, 7-isocyanoamphilecta-11(20),15-diene (12) and 7-isocyano-15-isothiocyanatoamphilecta-11(20)-ene (13), that displayed little antimalarial activity also showed little inhibitory activity in these FP detoxification assays. These studies suggest that the active isonitrile compounds, like the quinoline antimalarials, exert their antiplasmodial activity by preventing FP detoxification. Molecular dynamics simulations performed with diisocyanoadociane (4) and axisonitrile-3 (2) allowed their different binding to FP to be distinguished.

11543688
Wright CW, Addae-Kyereme J, Breen AG, Brown JE, Cox MF, Croft SL, Gokcek Y, Kendrick H, Phillips RM, Pollet PL
Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents.
J Med Chem. 2001 Sep 13;44(19):3187-94.
The indoloquinoline alkaloid cryptolepine 1 has potent in vitro antiplasmodial activity, but it is also a DNA intercalator with cytotoxic properties. We have shown that the antiplasmodial mechanism of 1 is likely to be due, at least in part, to a chloroquine-like action that does not depend on intercalation into DNA. A number of substituted analogues of 1 have been prepared that have potent activities against both chloroquine-sensitive and chloroquine-resistant strains of Plasmodium falciparum and also have in common with chloroquine the inhibition of beta-hematin formation in a cell-free system. Several compounds also displayed activity against Plasmodium berghei in mice, the most potent being 2,7-dibromocryptolepine 8, which suppressed parasitemia by 89% as compared to untreated infected controls at a dose of 12.5 mg kg(-1) day(-1) ip. No correlation was observed between in vitro cytotoxicity and the effect of compounds on the melting point of DNA (DeltaT(m) value) or toxicity in the mouse-malaria model.

11141105
Wright CW, Marshall SJ, Russell PF, Anderson MM, Phillipson JD, Kirby GC, Warhurst DC, Schiff PL
In vitro antiplasmodial, antiamoebic, and cytotoxic activities of some monomeric isoquinoline alkaloids.
J Nat Prod. 2000 Dec;63(12):1638-40.
Twenty-one alkaloids have been assessed for activities against Plasmodium falciparum (multidrug- resistant strain K1) in vitro; 18 of these are reported for the first time. Two protoberberine alkaloids, dehydrodiscretine and berberine, were found to have antiplasmodial IC(50) values less than 1 M, while seven alkaloids-allocrytopine, columbamine, dehydroocoteine, jatrorrhizine, norcorydine, thalifendine, and ushinsunine-had values between 1 and 10 M. These results are discussed in the context of structure-activity relationships. Compounds were also assessed for antiamoebic and cytotoxic activities, but none was significantly active except for berberine, which was moderately cytotoxic.

16269240
Wu X, Tiekink ER, Kostetski I, Kocherginsky N, Tan AL, Khoo SB, Wilairat P, Go ML
Antiplasmodial activity of ferrocenyl chalcones: investigations into the role of ferrocene.
Eur J Pharm Sci. 2006 Feb;27(2-3):175-87. Epub 2005 Nov 2.
A series of ferrocenyl chalcones were synthesized and evaluated in vitro against Plasmodium falciparum (K1) in a [3H] hypoxanthine uptake assay. Appropriate size, electronic, lipophilic and electrochemical parameters were determined for QSAR analysis. The results showed that the location of ferrocene influenced the ease of oxidation of Fe2+ in ferrocene and the polarity of the carbonyl linkage. These parameters were found to influence antiplasmodial activity. A general trend was noted in which compounds with ferrocene adjacent to the carbonyl linkage (series A) were associated with more selective and potent antiplasmodial activities. These compounds had polarized carbonyl linkages, lower lipophilicities and ferrocene rings that were less readily oxidized. The most active analogue was 1-ferrocenyl-3-(4-nitrophenyl)prop-2-en-1-one (28) (IC50 4.6 microM, selectivity index 37 against KB3-1 cells). To understand how the redox properties of ferrocene might influence antiplasmodial activity, the oxidant properties of selected compounds were investigated in antioxidant (ABTS+) and EPR experiments. The incorporation of ferrocene in the chalcone template was found to enhance its role in processes that involved the quenching and generation of free radicals. Thus, ferrocene may participate in redox cycling and this process may contribute to the antiplasmodial activity of ferrocenyl chalcones. However, the extent to which this property is manifested is also influenced by other physicochemical properties (lipophilicity, polarity, and planarity) of the compound.

16114082
Wube AA, Bucar F, Asres K, Gibbons S, Rattray L, Croft SL
Antimalarial compounds from Kniphofia foliosa roots.
Phytother Res. 2005 Jun;19(6):472-6.

During the course of screening Ethiopian medicinal plants for their antimalarial properties, it was found that the dichloromethane extract of the roots of Kniphofia foliosa Hochst. (Asphodelaceae), which have long been used in the traditional medicine of Ethiopia for the treatment of abdominal cramps and wound healing, displayed strong in vitro antiplasmodial activity against the chloroquine-sensitive 3D7 strain of Plasmodium falciparum with an ED50 value of 3.8 microg/mL and weak cytotoxic activity against KB cells with an ED50 value of 35.2 microg/mL. Five compounds were isolated from the roots and evaluated for their in vitro antimalarial activity. Among the compounds tested, 10-(chrysophanol-7'-yl)-10-(xi)-hydroxychrysopanol-9-anthrone and chryslandicin, showed a high inhibition of the growth of the malaria parasite, P. falciparum with ED50 values of 0.260 and 0.537 microg/mL, respectively, while the naphthalene derivative, 2-acetyl-1-hydroxy-8-methoxy-3-methylnaphthalene, exhibited a less significant antimalarial activity with an ED50 value of 15.4 microg/mL. To compare the effect on the parasite with toxicity to mammalian cells, the cytotoxic activities of the isolated compounds against the KB cell line were evaluated and 10-(chrysophanol-7'-yl)-10-(xi)-hydroxychrysopanol-9-anthrone and chryslandicin displayed very low toxicity with ED50 values of 104 and 90 microg/mL, respectively. This is the first report of the inhibition of the growth of P. falciparum by anthraquinone-anthrone dimers and establishes them as a new class of potential antimalarial compounds with very little host cell toxicity.

11145137
Yapi AD, Mustof M, Valentin A, Chavignon O, Teulade JC, Mallie M, Chapat JP, Blache Y
New potential antimalarial agents: synthesis and biological activities of original diaza-analogs of phenanthrene.
Chem Pharm Bull (Tokyo). 2000 Dec;48(12):1886-9.
Several diaza-analogs of phenanthrene derived from 3-amino, 5-amino, 6-amino, 8-aminoquinolines, and 5-aminoisoquinoline were prepared to evaluate their antiplasmodial activities. All compounds showed mild to good activitiy in vitro, both on a Nigerian chloroquino-sensitive strain and on the chloroquino-resistant FcB1-Columbia and FcM29 strains. The position of the intracyclic nitrogen atom is shown to be crucial for the activities (best results are obtained with a 1,10-phenanthroline skeleton). In regard to the particular properties of this structure (metalloprotease inhibition activitiy by chelating divalent metal ions), the potential chelating site of the molecule was blocked. In this case, the biological activity of the compound was greatly enhanced, showing that the mechanism of action of such a compound is probably not correlated to metalloprotease inhibition activity.

12898424
Yenesew A, Derese S, Irungu B, Midiwo JO, Waters NC, Liyala P, Akala H, Heydenreich M, Peter MG
Flavonoids and isoflavonoids with antiplasmodial activities from the root bark of Erythrina abyssinica.
Planta Med. 2003 Jul;69(7):658-61.
From the root bark of Erythrina abyssinica a new pterocarpene [3-hydroxy-9-methoxy-10-(3,3-dimethylallyl)pterocarpene] and a new isoflav-3-ene [7,4'-dihydroxy-2',5'-dimethoxyisoflav-3-ene] were isolated. In addition, the known compounds erycristagallin, licoagrochalcone A, octacosyl ferulate and triacontyl 4-hydroxycinnamate were identified. The structures were determined on the basis of spectroscopic evidence. The crude extract and the flavonoids and isoflavonoids obtained from the roots of this plant showed antiplasmodial activities.

14693228
Yenjai C, Prasanphen K, Daodee S, Wongpanich V, Kittakoop P
Bioactive flavonoids from Kaempferia parviflora.
Fitoterapia. 2004 Jan;75(1):89-92.
Nine flavonoids (1-9) have been isolated from Kaempferia parviflora. Among these, 5,7,4'-trimethoxyflavone (8) and 5,7,3',4'-tetramethoxyflavone (9) exhibited antiplasmodial activity against Plasmodium falciparum, with IC50 values of 3.70 and 4.06 microg/ml, respectively. 3,5,7,4'-Tetramethoxyflavone (7) and compound 8 possessed antifungal activity against Candida albicans with respective IC50 values of 39.71 and 17.63 microg/ml, and also showed mild antimycobacterial activity with the minimum inhibitory concentrations (MIC) of 200 and 50 microg/ml, respectively. However, none of the isolated compounds demonstrated cytotoxicity against KB, BC and NCI-H187 cell lines.

10821058
Yenjai C, Sripontan S, Sriprajun P, Kittakoop P, Jintasirikul A, Tanticharoen M, Thebtaranonth Y
Coumarins and carbazoles with antiplasmodial activity from Clausena harmandiana.
Planta Med. 2000 Apr;66(3):277-9.
Activity guided fractionation of extracts from Clausena harmandiana have led to the identification of four known compounds, heptaphylline (1), clausine K (2), dentatin (5), and clausarin (6). All these compounds, except clausine K (2), exhibited antiplasmodial activity against Plasmodium falciparum. While the new

dimethylated derivative 4, derived from 2, showed no antiplasmodial activity, the monomethylated product 3 (clausine H) exhibited activity comparable to that observed for compounds 1 and 5.

14697777
Ziegler HL, Franzyk H, Sairafianpour M, Tabatabai M, Tehrani MD, Bagherzadeh K, Hagerstrand H, Staerk D, Jaroszewski JW
Erythrocyte membrane modifying agents and the inhibition of Plasmodium falciparum growth: structure-activity relationships for betulinic acid analogues.
Bioorg Med Chem. 2004 Jan 2;12(1):119-27.
The natural triterpene betulinic acid and its analogues (betulinic aldehyde, lupeol, betulin, methyl betulinate and betulinic acid amide) caused concentration-dependent alterations of erythrocyte membrane shape towards stomatocytes or echinocytes according to their hydrogen bonding properties. Thus, the analogues with a functional group having a capacity of donating a hydrogen bond (COOH, CH(2)OH, CONH(2)) caused formation of echinocytes, whereas those lacking this ability (CH(3), CHO, COOCH(3)) induced formation of stomatocytes. Both kinds of erythrocyte alterations were prohibitive with respect to Plasmodium falciparum invasion and growth; all compounds were inhibitory with IC(50) values in the range 7-28 microM, and the growth inhibition correlated well with the extent of membrane curvature changes assessed by transmission electron microscopy. Erythrocytes pre-loaded with betulinic acid or its analogues and extensively washed in order to remove excess of the chemicals could not serve as hosts for P. falciparum parasites. Betulinic acid and congeners can be responsible for in vitro antiplasmodial activity of plant extracts, as shown for Zataria multiflora Boiss. (Labiatae) and Zizyphus vulgaris Lam. (Rhamnaceae). The activity is evidently due to the incorporation of the compounds into the lipid bilayer of erythrocytes, and may be caused by modifications of cholesterol-rich membrane rafts, recently shown to play an important role in parasite vacuolization. The established link between erythrocyte membrane modifications and antiplasmodial activity may provide a novel target for potential antimalarial drugs.

15388483
Ziegler HL, Hansen HS, Staerk D, Christensen SB, Hagerstrand H, Jaroszewski JW
The antiparasitic compound licochalcone a is a potent echinocytogenic agent that modifies the erythrocyte membrane in the concentration range where antiplasmodial activity is observed.
Antimicrob Agents Chemother. 2004 Oct;48(10):4067-71.
The well-known antiparasitic compound licochalcone A is a potent membrane-active agent that transforms normal erythrocytes into echinocytes in parallel with the inhibition of growth of Plasmodium falciparum cultures, the in vitro antiplasmodial effect apparently being an indirect effect on the host cell. In vitro experiments with synchronous cultures demonstrate that inhibition of invasion is the principal mechanism of growth inhibition. The erythrocyte membrane-modifying effect was also transiently observed in vivo in mice after intravenous administration.

12094303
Ziegler HL, Jensen TH, Christensen J, Staerk D, Hagerstrand H, Sittie AA, Olsen CE, Staalso T, Ekpe P, Jaroszewski JW
Possible artefacts in the in vitro determination of antimalarial activity of natural products that incorporate into lipid bilayer: apparent antiplasmodial activity of dehydroabietinol, a constituent of Hyptis suaveolens.
Planta Med. 2002 Jun;68(6):547-9.
Dehydroabietinol isolated from Hyptis suaveolens (L.) Poit. was found to inhibit growth of chloroquine-sensitive as well as chloroquine-resistant strains of Plasmodium falciparum cultivated in erythrocytes in vitro (IC 50 26-27 microM). However, erythrocytes exposed to dehydroabietinol were transformed in a dose-dependent manner towards spherostomatocytic forms with concomitant formation of endovesicles, as disclosed by transmission electron microscopy. The erythrocyte shape alterations caused by dehydroabietinol correlated well with its apparent IC 50 value. Thus, dehydroabietinol incorporates into the erythrocyte membrane, and since invasion and survival of Plasmodium parasites is known to depend on the function of the erythrocyte membrane, the observed antiplasmodial effect of dehydroabietinol is presumably an indirect effect on the host cell. Because of these findings, microscopic investigations should be generally used to support claims of antimalarial effects of apolar natural products.

11959580
Ziegler HL, Staerk D, Christensen J, Hviid L, Hagerstrand H, Jaroszewski JW
In vitro Plasmodium falciparum drug sensitivity assay: inhibition of parasite growth by incorporation of stomatocytogenic amphiphiles into the erythrocyte membrane.
Antimicrob Agents Chemother. 2002 May;46(5):1441-6.
Lupeol, which shows in vitro inhibitory activity against Plasmodium falciparum 3D7 strain with a 50% inhibitory concentration (IC50) of 27.7 +/- 0.5 microM, was shown to cause a transformation of the human erythrocyte shape toward that of stomatocytes. Good correlation between the IC50 value and the membrane

curvature changes caused by lupeol was observed. Preincubation of erythrocytes with lupeol, followed by extensive washing, made the cells unsuitable for parasite growth, suggesting that the compound incorporates into erythrocyte membrane irreversibly. On the other hand, lupeol-treated parasite culture continued to grow well in untreated erythrocytes. Thus, the antiplasmodial activity of lupeol appears to be indirect, being due to stomatocytic transformation of the host cell membrane and not to toxic effects via action on a drug target within the parasite. A number of amphiphiles that cause stomatocyte formation, but not those causing echinocyte formation, were shown to inhibit growth of the parasites, apparently via a mechanism similar to that of lupeol. Since antiplasmodial agents that inhibit parasite growth through erythrocyte membrane modifications must be regarded as unsuitable as leads for development of new antimalarial drugs, care must be exercised in the interpretation of results of screening of plant extracts and natural product libraries by an in vitro Plasmodium toxicity assay.

15863333
Zirihi GN, Grellier P, Guede-Guina F, Bodo B, Mambu L
Isolation, characterization and antiplasmodial activity of steroidal alkaloids from Funtumia elastica (Preuss) Stapf.
Bioorg Med Chem Lett. 2005 May 16;15(10):2637-40.
Bioassay-guided fractionation of the EtOH extract of the stem bark of Funtumia elastica resulted in the isolation of four steroidal alkaloids, holarrhetine (1), conessine (2), holarrhesine (3) and isoconessimine (4). Their structures were determined on the basis of 1D- and 2D-NMR techniques and mass spectrometry. Compounds 1-4 exhibited in vitro antiplasmodial activity against the chloroquine-resistant strain FcB1 of Plasmodium falciparum with IC50 values ranging from 0.97 to 3.39 microM. They showed weak cytotoxicity against a rat cell line L-6 with IC50 values ranging from 5.13 to 36.55 microM.

15814260
Zirihi GN, Mambu L, Guede-Guina F, Bodo B, Grellier P
In vitro antiplasmodial activity and cytotoxicity of 33 West African plants used for treatment of malaria.
J Ethnopharmacol. 2005 Apr 26;98(3):281-5.
Thirty-three plants commonly used in West tropical Africa by traditional healers for the treatment of malaria were collected and ethanolic extracts were obtained by decoction. The antiplasmodial activity of extracts was evaluated in vitro against the chloroquine-resistant FcB1 strain of Plasmodium falciparum. Cytotoxicity was determined on the human MRC-5 and the rat L-6 cell lines. Of the 33 plant extracts, eight (24.5%) showed significant antimalarial activity (IC(50) values ranging from 2.3 to 13.7 microg/ml), 14 (42.5%) weak activity (IC(50) values ranging from 15 to 50 microg/ml) and 11 (33%) appeared inactive (IC(50) values >50 microg/ml). Five plants were of particular interest, associating good antiplasmodial activity and weak cytotoxicity. These five included Nauclea latifolia with known antiplasmodial activity and four, Fagara macrophylla, Funtumia elastica, Phyllanthus muellerianus and Rauvolfia vomitoria, for which the description of antiplasmodial activity is entirely novel.