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Indoloquinoline Alkaloids as Antimalarials: Advances, Challenges, and Opportunities

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Dedicated to Professor Santosh G. Tilve on the Occasion of his 65th Birthday

Abstract: Malaria infections affect almost half of the world's population, with over 200 million cases reported annually. *Cryptolepis sanguinolenta*, a plant native to West Africa, has long been used across various regions of Africa for malaria treatment. Chemical analysis has revealed that the plant is abundant in indoloquinolines, which have been shown to possess antimalarial properties. Cryptolepine, neocryptolepine, and isocryptolepine are well-studied indoloquinoline alkaloids known for their potent antimalarial activity. However, their structural rigidity and associated cellular toxicity are major drawbacks for preclinical development. This review focuses on the potential of indoloquinoline alkaloids (cryptolepine, neocryptolepine, and isocryptolepine) as scaffolds in drug discovery. The article delves into their antimalarial effects in vitro and in vivo, as well as their proposed mechanisms of action and structure-activity relationship studies. Several studies aim to improve these leads by reducing cytotoxicity while preserving or enhancing antimalarial activity and gaining insights into their mechanisms of action. These investigations highlight the potential of indoloquinolines as a scaffold for developing new antimalarial drugs.

Keywords: Antimalarial, Alkaloid, Indoloquinoline, Cryptolepine, Neocryptolepine, Isocryptolepine, Natural Products.

Table of Contents

1. Introduction:

Malaria continues to be a significant public health concern globally. According to the World Health Organization (WHO), in 2022, there were about 249 million reported cases of malaria in 85 countries, resulting in the death of 608,000 individuals worldwide.[1] The majority of these fatalities were children under the age of five and pregnant women living in sub-Saharan Africa. This highlights the urgent need for continued efforts to control and prevent the spread of malaria, particularly in areas where the disease remains endemic. Malaria, a mosquito-borne disease, is one of the lethal human parasitic infections caused by *Plasmodium* species, namely *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. The most widespread and deadliest species globally is *P. falciparum*, which can cause severe anemia, cerebral malaria, and other complications that can be fatal if not treated promptly. *P. vivax*, found in Central and South America, Africa, and Asia, is the second most common species.[1-2] Although it is less lethal than *P. falciparum*, it can still cause long-term health problems and relapses if not treated effectively. Female *Anopheles* mosquitoes transmit *Plasmodium* parasites by feeding on the blood of an infected human and later infecting another human (Figure 1).[3] When the infected mosquito bites a human, it injects sporozoites into the bloodstream. The sporozoites travel to the liver and enter hepatocytes, where they undergo asexual reproduction, producing thousands of merozoites. These merozoites then enter the bloodstream and infect red blood cells, causing them to replicate. Some merozoites will mature into male and female gametocytes and infect the mosquito when it feeds on the person's blood. Symptoms of malaria usually appear 7-10 days after being bitten by an infected mosquito. Some types of malaria infection caused by *P. vivax* and *P. ovale* have dormant forms called hypnozoites, which can reactivate years after the initial infection if not treated properly.[3b]

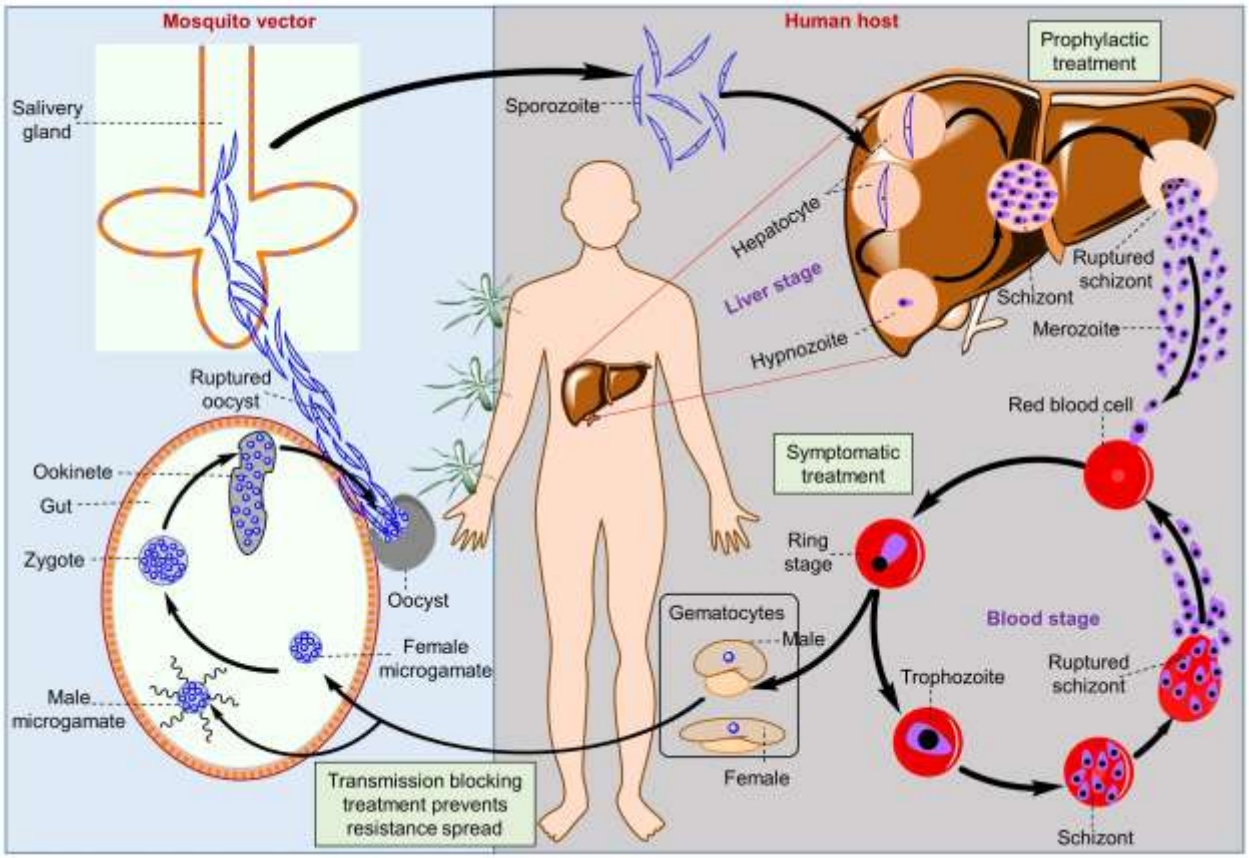

Figure 1: Schematic representation of the malaria life cycle. This image was reused from our previous publication with permission from Ref. [3a]. Copyright 2024, American Chemical Society.

Many drugs that we use today are closely related to natural products. Most of these drugs are either directly derived from natural sources, synthesized from partially modified natural products, or designed by optimizing the pharmacophore of a natural product.[4] Notably, over 63% of small-molecule drugs approved by the FDA have their roots in natural products.[4] This highlights the importance of natural compounds in drug discovery and underscores the need to continue exploring nature's chemical diversity to develop new therapies. Malaria treatment has a rich tradition of utilizing natural remedies. Medicinal plants have been a source of two essential antimalarial agents: quinine and artemisinin. A range of medications, such as quinine, chloroquine, mefloquine, artemisinin, etc. (Figure 2),[4-5] have been employed for malaria treatment. Nevertheless, the disease-causing protozoans have developed resistance to numerous treatments, posing a significant challenge.[6] Due to the increase of drug resistance in *P. falciparum*, the WHO has recommended artemisinin-based combination therapies (ACTs) as the first-choice antimalarial treatment.[4, 7] However, this strategy requires high doses or days of

administration, and more drug-resistant strains have been reported.[8] Therefore, it is urgent to find new and effective treatment strategies for malaria.

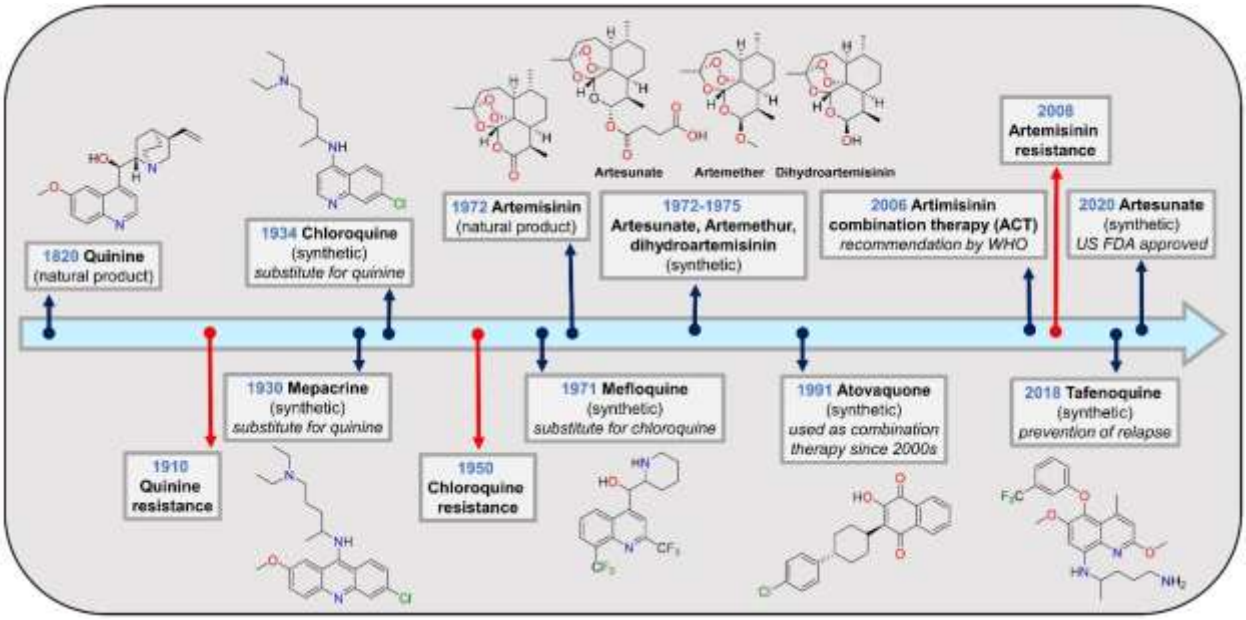

Figure 2: Timeline of key developments in antimalarial drugs associated with plant-derived natural and synthetic molecules.

For many years, the plants have been utilized in African traditional medicine (ATM) to treat malaria and fevers.[9] Thus, there is a growing interest in using natural products as malaria treatments or as a foundation for developing new antimalarial drugs.

3 Extracts of *Cryptolepis sanguinolenta* to treat malaria:

The roots of *Cryptolepis sanguinolenta*, an indigenous West African plant, have been revered for their medicinal properties for the last several decades. This plant is a rich source of indoloquinoline alkaloids. In Central and West Africa, the roots of this plant have been used in traditional medicine to treat various non-infectious and infectious diseases, including malaria.[10] In clinical therapy, a decoction from this plant has been used to treat urinary tract infections, rheumatism, and malaria since 1974.[11] The plant is predominantly discovered on the Akwapim and Kwahu mountain ranges in Ghana and the country's Central, Volta, and Western regions.[12] In Ghana, this plant is commonly known as "Ghana quinine." In other regions, it's referred to by various names, such as nurubima (Guans), kadze (Ewe), and nibima (Twi). It is a popular ingredient among traditional healers and is often found in various herbal products in Ghana, such

as Class Malacure, Herbaquine, Nibima, Phyto-Laria, and Malaherb.[13] A clinical study evaluated the effectiveness of Phyto-Laria on patients aged 11 years and above who displayed clinical symptoms of malaria and were diagnosed via blood film examination.[14] The study found that all patients demonstrated clearance of parasitemia within a week. Nonetheless, two patients exhibited recrudescence within 28 days, possibly due to re-infection.

Pousset and co-workers[15] conducted a series of carefully planned experiments to investigate whether the aqueous root extracts of *C. sanguinolenta* have inhibitory effects on different strains of *P. falciparum* that exhibit varying levels of resistance to chloroquine (CQ). The experiments were conducted in vitro and included testing the CQ-sensitive strain F32/Tanzania (IC_{50} CQ = 0.025 μM) as well as the CQ-resistant strains FcB1/Colombia (IC_{50} CQ = 0.205 μM) and FcR3/Gambia (IC_{50} CQ = 0.422 μM). The results of the experiments showed that the aqueous extracts had a significant inhibitory effect on the in vitro growth of all strains of *P. falciparum*, regardless of their resistance to chloroquine with IC_{50} ranging between 1 to 2 μg/mL. These results indicate that the aqueous root extracts of *C. sanguinolenta* possess potent inhibitory properties and may serve as a promising candidate for future antimalarial treatments.

Studies conducted by Cimanga and his team[16] explored the antiplasmodial activity of three different extracts from the root bark of *C. sanguinolenta* through in vitro testing against *P. falciparum* strains D6, K1, and W2. The results showed that all *C. sanguinolenta* root bark extracts exhibited promising antiplasmodial activity against the *P. falciparum* CQ-sensitive strain D6. Of these, the total alkaloid fraction (F3) demonstrated the best activity with an IC_{50} value of 47 ± 2.0 ng/mL. The 80% EtOH extract (F2) also showed a more pronounced antiplasmodial activity (IC_{50}, 72 ± 1.5 ng/mL) compared to the aqueous extract (F1) (IC_{50}, 122 ± 1.9 ng/mL). Regarding the two *P. falciparum* CQ-resistant strains K1 and W2, extract F3 showed strong antiplasmodial activity with IC_{50} values of 42 ± 0.1 and 54 ± 0.7 ng/mL, respectively. Extract F2 (IC_{50}, 56 ± 0.1 ng/mL) also exhibited a more pronounced antiplasmodial activity. However, the aqueous extract (F1) was the least active in all cases.

Paulo's group[17] conducted an in vitro study on the efficacy of *C. sanguinolenta* extracts from leaves and roots in combating the multidrug-resistant strain K1 and CQ-sensitive T996 clone of *P. falciparum*. The study found that all extracts were able to inhibit 90% of *P. falciparum* K1 growth at concentrations below 23 μg/mL. Interestingly, the root extracts were more effective than the leaf extracts. Additionally, two out of three samples showed higher activity in their ethanolic extracts compared to their aqueous counterparts.

3. Indoloquinoline alkaloids: cryptolepine, neocryptolepine, and isocryptolepine

3.1 Isolation and structural features:

Indoloquinoline alkaloids are tetracyclic heteroaromatic compounds comprising indole and quinoline rings fused through pyrrole and pyridine rings. This specific arrangement of rings allows only four isomeric ring systems, which are indolo[3,2-*b*]quinoline **1**, indolo[2,3-*b*]quinoline **2**, indolo[3,2-*c*]quinoline **3**, and indolo[2,3-*c*]quinoline **4**, as depicted in Figure 3a.[18] The natural indoloquinolines are limited to ring systems **1** - **3**, while no natural products belonging to ring system **4** have been found (Figure 3b), although its framework has been synthesized.[18b]

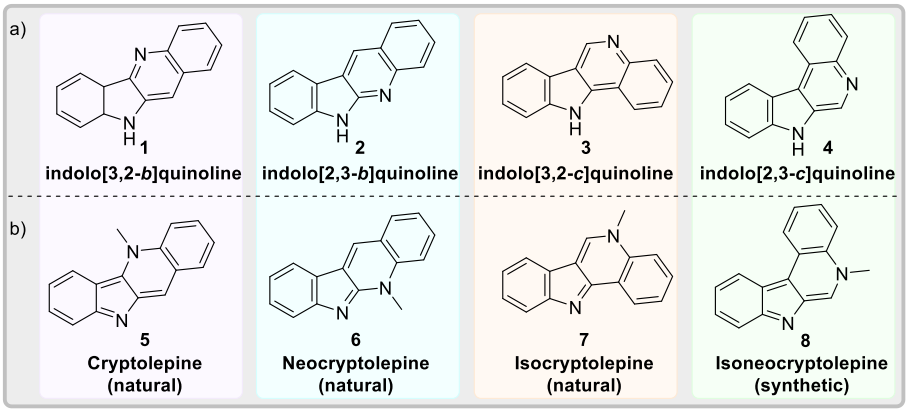

Figure 3: Chemical structures of – a) indoloquinoline ring systems **1** – **4**; b) natural and synthetic indoloquinolines **5** – **8** belonging to each ring systems **1** - **4**.

Several indoloquinoline alkaloids, including cryptolepine **5**, neocryptolepine **6**, and isocryptolepine **7** (as shown in Figure 3b), have been isolated from the roots of *C. sanguinolenta*. Cryptolepine **5** was first isolated from *C. triangularis* in 1929[19] but was later discovered in the roots of *C. sanguinolenta* in 1951 by Gellert et al.[20] Isocryptolepine **7**, a related alkaloid, was independently discovered by two research groups in 1995, which named it cryptosanguinolentine[21] and isocryptolepine,[22] respectively. While cryptolepine **5** has a linearly-fused indolo[3,2-*b*]quinoline **1** ring system, isocryptolepine **7** has an angularly-fused indolo[3,2-*c*]quinoline **3** ring system. In 1996, two independent research groups discovered a new alkaloid **6** containing linearly-fused indolo[2,3-*b*]quinoline **2** ring system, which they named neocryptolepine[23] and cryptotackieine,[21] respectively.

3.2 General biological activities:

The tetracyclic indoloquinolines have been the subject of extensive research due to their remarkable range of biological activities and high binding affinity to various nucleic acids. These compounds exhibit tremendous potential for use in different therapeutic applications owing to their unique chemical structure and diverse pharmacological properties. Recent findings have demonstrated that indoloquinolines and their analogs possess potent biological activity, indicating their potential as lead compounds in the fight against infectious diseases and cancer.[24] In particular, indoloquinoline alkaloids **5** - **7** have displayed high efficacy in combating CQ-resistant *P. falciparum* - a significant challenge in malaria treatment, and cryptolepine has been used as a lead compound.[25] These alkaloids intercalate with DNA's double helix structure, causing changes in conformation and inhibiting replication and transcription.[26] The strength and mode of binding of these alkaloids to DNA have been studied using spectroscopy and X-ray analysis.[27] Among the different indoloquinolines, cryptolepine binds to DNA 10 times more tightly and is more cytotoxic towards B16 melanoma cells.[27a] Indoloquinoline alkaloids and their analogs have shown various other biological activities, including antimuscarinic, antibacterial, antifungal, antiviral, antimycotic, anti-inflammatory, hypotensive, antihyperglycemic, and antitumor activity.[10d, 18a, 24a, 24c-e, 28] Although the exact cellular targets of indoloquinolines and their various mechanisms of action within a cell are not fully understood, their high affinity for binding to DNA in vitro suggests that DNA may be a critical target for these compounds.

3.3 Total and formal synthesis:

Indoloquinolines' intriguing structural characteristics and varied biological activities have captivated the scientific community. Cryptolepine, neocryptolepine, and isocryptolepine the main indoloquinolines derived from *C. sanguinolenta*, have received significant attention due to their interesting structural features and wide range of biological activities. There has been a recent surge in interest among researchers in synthesizing these isomeric indoloquinoline alkaloids and their derivatives. Several review articles[10c, 18, 29] have been published to provide insight into the total and formal synthesis of indoloquinolines. The most recent article, published in 2022,[18b] is noteworthy for its comprehensive overview of the current synthetic strategies and methods available in the literature. The authors have comprehensively compiled the various synthetic methods reported in the literature on constructing four essential indoloquinoline skeletons, **1**-**4**. In this section, we summarized the different methods used to synthesize cryptolepine,

neocryptolepine, isocryptolepine, and their precursor compounds (de-methylated indoloquinolines), highlighting the key reactions (Table 1-3).

Table 1: Overview of total/formal synthesis of cryptolepine and analogs.

Key reaction(s)	Ref.
a) **Formation of the quinoline ring**	
• Base-mediated cyclization	[30]
• Vilsmeier-Haack reaction/intramolecular cyclization	[31]
• Intramolecular β-nucleophilic substitution	[32]
• Nucleophilic cyclization	[33]
• One-pot reduction-cyclization-aromatization	[34]
• Tandem reductive cyclization-dehydration	[35]
b) **Formation of the indole ring**	
• Rh-catalyzed amination/intramolecular cyclization	[36]
• Pd-catalyzed Buchwald-Hartwig reaction	[37]
• Cu-catalyzed coupling reaction/Pd-catalyzed intramolecular arylation	[38]
• Buchwald-Hartwig amination/intramolecular Heck-type reaction	[39]
• [3+3] annulation	[40]
• Bi-catalyzed-arylation/Pd-catalyzed oxidative cyclization	[41]
• Mo-catalyzed Cadogon cyclization	[42]
• Friedländer/Buchwald-Hartwig reaction	[43]
c) **Formation of the quinoline/indole rings**	
• PPA-mediated intramolecular cyclization	[44]
• Cu-catalyzed cyclization/reduction/cyclization	[45]
• Reductive Cadagon cyclization	[46]
• Buchwald-Hartwig reaction/nitrene insertion	[47]
• DDQ-mediated oxidative cyclization	[48]

Table 2: Overview of total/formal synthesis of neocryptolepine and analogs

Key reaction(s)	Ref.
a) **Formation of quinoline ring**	
• I_2-mediated Friedel-Crafts alkylation/oxidative coupling	[49]
• PivOH-mediated alkylation-dehydration-cyclization	[50]
• Electrophile-triggered cross-amination/Friedel-Crafts alkylation	[51]
• $FeCl_3$-mediated Friedel-Crafts alkylation/oxidative cyclization	[52]
• Photocatalytic aerobic oxygenation	[53]
• One-pot imination-nucleophilic addition-annulation	[54]
• Friedel-Crafts type reaction	[55]
• I+/TBHP-mediated tandem oxidative cyclization-aromatization	[56]
• PPh_3-mediated one-pot reduction-cyclization-aromatization	[57]
• Pd-catalyzed C-H activation	[58]
• Rd-catalyzed C-C/C-N coupling	[59]
• Acid-mediated coupling	[60]
• Conjugate addition/heterocyclization	[61]
• Aldol condensation/one-pot reduction-cyclization	[62]
• $SnCl_2$-mediated reduction/cyclization	[63]
• Alkylation/rearrangement/reductive cyclization	[64]
• DDQ-mediated oxidative cyclization	[65]
• Domino alkylation-reduction-cyclization	[66]
• I_2-mediated annulation	[67]
• Visible-light-induced intramolecular oxidative cyclization-detosylation-aromatization	[68]
b) **Formation of indole ring**	
• Pd-catalyzed Suzuki coupling/cyclization	[69]
• Graebe-Ullmann reaction	[70]
• One-pot condensation-Pd-catalyzed intramolecular arylation	[71]
• Pd-catalyzed cross-coupling/thermal cyclization	[72]
• Pd-catalyzed Buchwald-Hartwig C-N coupling	[73]
• Photo-induced nitrene insertion	[74]

c) **Formation of quinoline/indole rings**

- Domino N_2-extrusion-cyclization [75]
- Intramolecular Diels-Alder reaction [76]
- Aza-Wittig/electrocyclic ring closure [77]
- Thermal biradical cyclization [78]
- Ag_2CO_3-mediated cascade annulation [79]
- Intramolecular Wittig reaction [80]
- Au-catalyzed annulation [81]
- Double reductive cyclization [82]
- Suzuki coupling/DDQ-mediated C-H amination [48]
- Chloride-ion-triggered 6-endo cyclization [83]
- Pd-catalyzed dual annulation [84]
- Pd-catalyzed cascade cyclization [85]
- $Cu(OTf)_2$-mediated heteroannulation [86]
- Pd-catalyzed double annulation [87]
- Rh-catalyzed coupling/intramolecular [4+2] cycloaddition [88]

Table 3: Overview of total/formal synthesis of isoocryptolepine and analogs

Key reaction(s)	Ref.
a) **Formation of the quinoline ring**	
• Pd-catalyzed Ullmann cross-coupling	[89]
• Radical-mediated cyclization	[90]
• Pd-catalyzed intramolecular Heck coupling	[91]
• Intramolecular dehydrogenative coupling	[92]
• 4-component Ugi reaction/Pd-catalyzed cyclization	[93]
• Cu-mediated intermolecular cascade C-H/N-H annulation	[94]
• Chemoselective cycloimidoylation	[95]
• Tb-doped-TiO_2-mediated domino reaction	[96]
• Photo-induced aerobic tandem dehydrogenative Povarov/aromatization reaction	[97]

• SnCl4-mediated intramolecular electrophilic amination	[98]
• Oxidative intramolecular dearomative spirocyclization	[99]
b) **Formation of the indole ring**	
• Cu-catalyzed coupling/Pd-catalyzed intramolecular arylation	[100]
• Buchwald-Hartwig amination/intramolecular Heck-type reaction	[39,101]
• Photocyclization	[102]
• Suzuki-Miyaura cross-coupling/azidation/thermally induced nitrene insertion	[74]
c) **Formation of the quinoline/indole rings**	
• Fisher indole synthesis	[103]
• Electrophilic cyclization/Buchwald-Hartwig amination	[104]
• Au-catalyzed C-N cross-coupling	[105]
• Rh-catalyzed dimerization	[106]
• PPA-mediated Michael-type addition/rearrangement	[107]
• TfOH-mediated *N*-heteroannulation	[108]
• Rh-catalyzed C-H functionalization/cyclization	[109]

3.4 In vitro and in vivo antimalarial activities:

Cryptolepine is a well-researched indoloquinoline with promising activity against various strains of *P. falciparum*. In 1991, Noamesi et al.[110] discovered that cryptolepine, extracted from the roots of *C. sanguinolenta*, showed potent in vitro antimalarial activity against the multi-resistant K1 strain of *P. falciparum*. Its IC_{50} value of 134 nM was comparable to chloroquine (IC_{50} = 230 nM). When administered orally to infected mice, cryptolepine also demonstrated significant in vivo activity against *P. berghei yoelii* and *P. berghei berghei*. However, it showed no significant efficacy when administered subcutaneously to infected mice with *P. berghei* strain NK65 at nontoxic doses.[16, 111] Kirby and co-workers[111] tested cryptolepine's in vivo antimalarial activity at different doses but found no significant effect on *P. berghei* infection in mice. In vivo studies conducted by Cimanga et al.[16] on infected mice found that cryptolepine as its hydrochloride, effectively suppressed *P. berghei yoelii* and *P. berghei berghei*, while the free form of cryptolepine only had an effect against *P. berghei yoelii*.

Over the years, other researchers have reported the antimalarial activity of cryptolepine, neocryptolepine, and isocryptolepine against CQ-resistant and CQ-sensitive strains of *P. falciparum* (Table 4-6).

Table 4: In vitro antimalarial activity of cryptolepine against different strains of *P. falciparum*.

***P. falciparum* strains**	**IC_{50} (nM)**	**Ref.**
K1	142.07 ± 0.1, 440 ± 0.22, 134 ± 0.04, 230 ± 0.004, 440 ± 0.22, 114 ± 0.06, 120 ± 0.02 (SI = 9.33 – L6/K1)	[16],[112],[111], [17],[113], [114],[115]
W2	176.51 ± 0.5, 755 ± 1/1.4 (Vero/W2), 1808.16 (SI = 10 – Vero/W2), 2000 ± 0.1	[16],[44a],[116],[117]
FcB1	430 ± 0.23	[118]
FcR3	440	[118]
V1/S	424 ± 78	[44a],
D6	116.24 ± 0.3, 222 ± 5, 774.92 (SI = 23.3 – Vero/D6)	[16],[44a],[116],
3D7	460 ± 0.04 (SI = 101 - HepG/3D7), 603.82 ± 75.57, 259 ± 29,	[112],[119],[120],[44a]
HB3	270 ± 0.06,	[121]
Ghana	2300 ± 0.6	[117]

SI is the ratio of IC_{50} for cytotoxicity versus antiplasmodial activity.

Table 5: In vitro antimalarial activity of neocryptolepine against different strains of *P. falciparum*.

P. falciparum strains	IC_{50} (nM)	Ref.
K1	219.56 ± 0.1, 1696 (SI = 1.88 – L6/K1), 2610 ± 0.67 (SI = 1.24 – L6/K1),	[16],[122],[123],[115]
W2	279.83 ± 1.3, 14000 ± 1.7 (SI = 0.78 - MRC-5/W2),	[16],[124],[117]

NF54	1580 (SI = 2.0 – L6/NF4),	[122],[125],[123]
D6	150.68 ± 0.7,	[16],
Ghana	27300 ± 5.7 (SI = 0.4 – MRC-5/Ghana),	[124],[117]

SI is the ratio of IC_{50} for cytotoxicity versus antiplasmodial activity.

Table 6: In vitro antimalarial activity of isocryptolepine against different strains of *P. falciparum*.

P. falciparum strains	IC_{50} (nM)	Ref.
K1	778.6 ± 86.5 (SI = 10.72 – MRC-5/K1), 780 (SI = 1.52 – L6/K1), 17 ± 0.004 (SI = 747.06 – L6/K1)	[126],[127],[115],
SKF58	410 ± 4.8 (SI = 20.37 – MRC-5/ SKF58),	[126]
SRIV35	462.8 ± 16.5 (SI = 18.04 – MRC-5/SRIV35),	[126]
FcB1	300	[118]
W2mef	1177 ± 390 (SI = 1.9 – 3T3/W2mef)	[128]
3D7	585 ± 50.1 (SI = 14.27 – MRC-5/3D7), 148.31 ± 22.87, 1211 ± 84 (SI = 1.7 – HEK293/3D7),	[126],[129],[130],[128]

SI is the ratio of IC_{50} for cytotoxicity versus antiplasmodial activity.

Table 7: Comparison of in vitro antimalarial activity of cryptolepine, neocryptolepine, and isocryptolepine with chloroquine and artemisinin against *P. falciparum* K1 strain [115].

Compounds	*P. falciparum* K1 strain IC_{50} (nM)	SI (L6/K1)
Cryptolepine	120	9.33

Neocryptolepine	2610	1.24
Isocryptolepine	780	1.52
Chloroquine	170	-
Artemisinin	42	-

SI is the ratio of IC_{50} for cytotoxicity versus antiplasmodial activity.

Indoloquinolines show great potential as antimalarial agents, but their practical application comes with significant challenges. One major obstacle is improving their selectivity towards the target parasite while retaining their potency. To overcome this hurdle, a comprehensive understanding of their mode of action is essential, which can aid in maximizing their therapeutic efficacy.

3.5 Mode of action:

Several in vitro tests and functional assays were used to gain insight into the mechanism of action of the antimalarial activity of the indoloquinolines.[112, 117, 131] These studies indicate that indoloquinolines exhibit antimalarial activity through a combination of two mechanisms: inhibiting the formation of β-hematin (similar to chloroquine)[131b] and interacting with DNA.[117, 131b-d]

Quinoline antimalarial compounds, like chloroquine,[131a] work by inhibiting the formation of β-hematin in the acidic food vacuole of the parasite. This disruption stops the conversion of the toxic by-product of hemoglobin digestion into harmless hemozoin, leading to cell lysis and death. The basic nitrogen in indoloquinolines enhances the compound's basicity,[11d, 30c,131a] allowing it to accumulate in the acidic food vacuole of the plasmodium parasite and exert its antimalarial activity.

In terms of DNA intercalation,[117, 131b-d] indoloquinolines position themselves between the G-tetrad and the neighboring Watson-Crick base pair at quadruplex-duplex (Q-D) junctions. This maximizes π-π stacking interactions and electrostatic interactions, impeding DNA replication and RNA transcription in the parasite due to the planarity of indoloquinolines, which enables them to intercalate with the DNA double helical structure.

While inhibiting the heme detoxification process is a selective mechanism, DNA intercalation is nonselective and contributes to cytotoxicity and activity against other parasites.[131c] The underlying mechanism of this toxicity is primarily attributed to their ability to intercalate with DNA, which results in the inhibition of DNA synthesis and the blocking of

topoisomerase II activity.[132] The unveiling of the crystal structure of the cryptolepine-DNA complex has confirmed that cryptolepine intercalates exclusively between non-alternating G-C sequences.[132b, 133] These results indicate that cryptolepine may not be a viable primary candidate for developing new antimalarial agents due to its limited specificity. However, the recent studies by Wright et al.[112] showed that the antiplasmodial mode of action of cryptolepine involves inhibition of β-hematin formation independent of interactions with DNA. This suggests the potential for synthesizing analogs of indoloquinolines that maintain antiplasmodial properties without intercalating into DNA.

3.6 Physicochemical properties and stability studies:

The acid-base dissociation constant, pKa, is a key feature associated with the biological activity of alkaloids. Grycová et al.[134] conducted a study to determine the pKa values of indoloquinoline alkaloids utilizing ^{1}H NMR spectroscopy in a mixture of solvents. It has been observed that pKa values are significantly dependent on the structure of the indoloquinolines and that there is a correlation between pKa and the bond separation between two nitrogen atoms. Studies have revealed that alkaloid cryptolepine has the highest recorded pKa value of 11.0 among three alkaloids with two nitrogen atoms separated by three chemical bonds. The calculated pKa value of cryptolepine is comparable to that of other published reports.[135] Conversely, isocryptolepine, with four chemical bonds between the nitrogen atoms, exhibited a lower pKa value of 9.8. The smallest pKa value of 7.1 was observed in neocryptolepine, where the nitrogen atoms are only two bonds apart.[134]

Cryptolepine, neocryptolepine, and isoneocryptolepine are isomeric compounds with the same molecular formula, $C_{16}H_{12}N_2$, and an average mass of 232.280 Da.

The stability studies[135a] conducted on cryptolepine indicate it is relatively stable in neutral and acidic environments. However, it is highly vulnerable to degradation in alkaline and oxidative conditions. Short-term stability has been observed when exposed to fluorescence light and dry heat at 60°C. Furthermore, the ionized form of cryptolepine is deemed more stable than its unionized counterpart.[135a]

4. Structure-activity relationship (SAR) studies:

Indoloquinoline alkaloids represent a noteworthy category of naturally occurring antimalarials, featuring a non-chiral skeleton and uncomplicated chemical structures that ease their total synthesis. Furthermore, their chemical diversity can be readily incorporated. In recent

decades, various structural modifications have been made to these alkaloids to enhance antimalarial activity, improve the selectivity index, and better understand their mechanism of action. This section discusses the SAR studies on the antimalarial activity of isomeric indoloquinolines, namely cryptolepine, neocryptolepine, and isocryptolepine.

4.1 Cryptolepine:

Extensive research has demonstrated that cryptolepine exhibits exceptional antimalarial activities both in vitro and in vivo. However, it is important to note that cryptolepine can also intercalate with DNA, which may lead to harmful cytotoxic effects. Wright and his team[136] synthesized different analogs of cryptolepine and assessed their antiplasmodial activities against CQ-sensitive HB3 and CQ-resistant K1 strains of *P. falciparum*. They found that the *N*-demethylated analogs of cryptolepine were ineffective, suggesting that the 5-methyl group in cryptolepine is essential for its antiplasmodial activity. Some of the analogs synthesized demonstrated similar or improved potency compared to cryptolepine. Furthermore, all halogenated analogs were more potent than cryptolepine, with 2,7-dibromocryptolepine **9a** being the most effective (Figure 4). Several analogs also exhibited activity against *P. berghei* in mice, where 2,7-dibromocryptolepine **9a** suppressed parasitemia by 89% at a dose of 12.5 mg/kg/day, with no apparent toxicity to the mice. In addition, some potent analogs inhibited β-hematin formation, indicating a chloroquine-like mode of action, at least in part.

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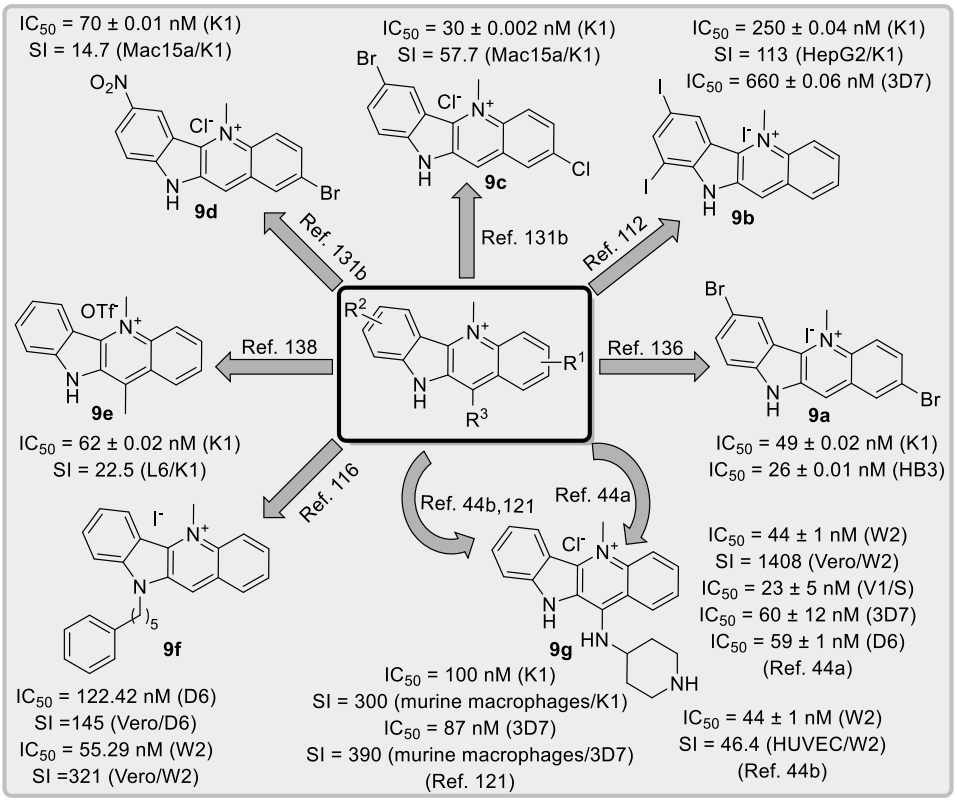

Figure 4: Antimalarial activities of cryptolepine analogs.

In a separate study by the same team,[137] several cryptolepine analogs comprising alkyl, alkoxy, halogen, or nitro groups were synthesized and assessed against the *P. falciparum* K1 strain. The study found that analogs with a halogen in the quinoline ring and a halogen or a nitro group in the indole ring exhibited better antiplasmodial activity. The 7-bromo-2-chlorocryptolepine **9c** and 2-bromo-7-nitrocryptolepine **9d** (Figure 4) were the most potent and selective analogs. These two analogs suppressed parasitemia by more than 90% at doses of 25 mg/kg/day, with no apparent toxicity to the mice. The study also evaluated the effects of these analogs on inhibiting β-hematin formation. However, there was no correlation between the antiplasmodial activities and the inhibition of hemozoin formation, indicating that the potent antimalarial activity of the cryptolepine analogs involves other mechanisms besides the inhibition of hemozoin formation. More recently,[112] the same group semi-synthesized the analogs of cryptolepine and tested their antimalarial activity against CQ-sensitive and CQ-resistant *P. falciparum* asexual blood-stage parasites. Semi-synthetic analogs showed either similar or better activity against the *P. falciparum* chloroquine- and pyrimethamine-resistant strain K1, with some analogs being 1.8-3 times more potent than the cryptolepine. Although none of these semi-synthetic analogs exhibited the same level of efficacy as the previously reported 2,7-dibromo derivative **9a**, analog **9b** showed relatively

higher selectivity towards HepG2 cells (Figure 4). All analogs demonstrated similar antiplasmodial activities as that of cryptolepine against CQ-sensitive *P. falciparum* strain 3D7 and the zoonotic parasite *P. knowlesi*.

Rocca's group[138] modified the structure of cryptolepine at positions *N*-5 and *C*11 and tested the activity of these analogs against the *P. falciparum* CQ-resistant K1 strain. They found that methylation at position 5 is essential for the compound's activity, as quindoline was significantly less active and less selective than cryptolepine (Figure 4). Conversely, alkylation at the *C*11 position reduced the compound's activity, except for 11-methylcryptolepine **9e**, which was approximately 5 times more active than cryptolepine and displayed comparable selectivity (Figure 4). Fluorescence microscopy confirmed that the cryptolepine and analogs localized within parasite DNA-containing structures, such as the nucleus and kinetoplast. This strongly suggests that the compounds act on the parasite by interacting with DNA through a mechanism similar to the one proposed by Dassonneville et al.[139]

Moreira and colleagues[44b] focused on the *C*11 position of the cryptolepine and introduced short basic side chains to enhance its efficacy and selectivity against the *P. falciparum* W2 strain. Various cryptolepine analogs containing an alkyl diamine side-chain at *C*-11 were synthesized and evaluated for their antiplasmodial activity. The results showed that these analogs had better antiplasmodial activity than the parent compound, with IC_{50} values ranging from 22 to 184 nM. The analogs with 3-carbon side chains had better antiplasmodial activity than those with 2-carbon or 4-carbon atoms. Additionally, the analogs with branched side chains had a reduced activity regardless of the side-chain length. The most selective compound in this series was the piperidine analog **9g** (Figure 4), with a selectivity index of 46, and it was also the least cytotoxic of the series.

Later, two other research groups synthesized a series of cryptolepine analogs with basic side chains at the *C*11 position and tested their antiplasmodial activities against a panel of *P. falciparum* strains, including CQ-resistant K1 and W2, CQ-sensitive 3D7, CQ- and pyrimethamine-resistant V1/S, and CQ-sensitive, mefloquine-resistant D6. Paulo's group[44a] discovered several potent analogs that significantly increased the antiplasmodial activity against CQ-resistant and CQ-sensitive *P. falciparum* strains while having high selectivity compared to the parent compound, cryptolepine. The analog containing a conformationally restricted piperidine side-chain, **9g** (Figure 4), showed the best cytotoxicity profile, with a selectivity index of 1408. Pohlita et al.[121] evaluated the in vitro antimalarial activity of cryptolepine and 11-(4-piperidinamino)cryptolepine **9g** (Figure 4) against *P. falciparum* K1 and 3D7 strains (Figure 4), as well as in vivo studies in *P. berghei*-infected mice. Cryptolepine triflate only showed moderate oral

and subcutaneous activity at 50 mg/kg/day (43 - 63% inhibition, MST = 24 - 25 days), while cryptolepine derivative **9g** was lethal to infected mice (MST = 3 days) and oral activity at this dose was moderate (45 - 55% inhibition, MST = 25 days).

Ablordeppeya et al.[116] synthesized several *N*-substituted quindolines and evaluated some of the selected analogs for potency against the *P. falciparum* K1 strain. Of all the compounds tested, only **9f** (Figure 4) exhibited significantly higher potency against the *P. falciparum* K1 strain and had a higher selectivity index than the cryptolepine.

Further, various *N*,*O*-, *N*,*N*- and *O*-alkylated analogs of quindolines were analyzed for their antiplasmodial activity against the CQ-resistant *P. falciparum* W2 strain by Paulo's group.[140] The unsubstituted quindolones showed no activity, while the analogs with monosubstituted alkylamine showed weak or moderate activity. The introduction of two alkylamine side chains generally improved the antiplasmodial activity. The substitution by chlorine atoms at positions 3 and 7 of the quindolone skeleton improved antiplasmodial activity for *N*,*O*-bis-alkylamine analogs but not for *N*,*N*-disubstituted analogs. The most potent and selective analog was **10d** (Figure 5), which showed an IC_{50} of 51 nM and a good selectivity ratio of 98. Additionally, the proposed mechanism of action was investigated by determining equilibrium binding constants (Kass) with hematin monomer (FPIX-OH) using UV–vis titration at pH 5.5.[141] The results indicate that the mechanism is similar to chloroquine and acridone, i.e., the inhibition of hemozoin formation. In a subsequent year,[142] *N*5,*N*10-bis-alkylamine, and *N*10,*O*11-bis-alkylamine analogs of quindolone were studied to investigate the potential of targeting hemozoin crystals. These analogs' antimalarial cytostatic and cytocidal activities were studied against CQ-resistant W2 and CQ-sensitive 3D7 strains of *P. falciparum*. The bis-alkylamine analogs of both series displayed a wide range of cytostatic activities, with **10d** and **10a** (Figure 5) being the most active of each series. The growth inhibition resistance indices (giRI) ranged from <1 to 0.5−2. The *N*5,*N*10-bis-alkylamine analogs exhibited potent growth inhibition activity against the W2 strain, while the *N*10,*O*11-bis-alkylamine analogs showed potent parasite inhibition against both the W2 and 3D7 strains. The researchers also evaluated the cytocidal activity of selected analogs against *P. falciparum* 3D7 and Dd2 (CQ-resistant) strains, with varying levels of activity observed. Both series of analogs bound to hematin monomer inhibited β-hematin formation in vitro and delayed intraerythrocytic parasite development with apparent inhibition of hemozoin biocrystallization, with higher cytocidal activity against schizonts. In another report,[143] the same group designed and synthesized novel quindoline analogs (*N*10,*N*11-di-alkylamine bioisosteres) to improve their ability to access and bind to their target to treat malaria. These analogs showed strong antimalarial activity and were

selective for malaria parasites compared to human hepatic cells. The most effective analog **10b** (Figure 5), structurally similar to the existing antimalarial drug chloroquine, showed the highest antiplasmodial activity against a CQ-resistant strain of the malaria parasite. To better understand how these analogs work, the researchers calculated various properties of the compounds and evaluated their ability to inhibit the growth of hemozoin, a target for antimalarial drugs. The results suggest that these analogs inhibit the growth of hemozoin, which indicates that the inhibition of hemozoin growth is a possible mechanism of action for these analogs.

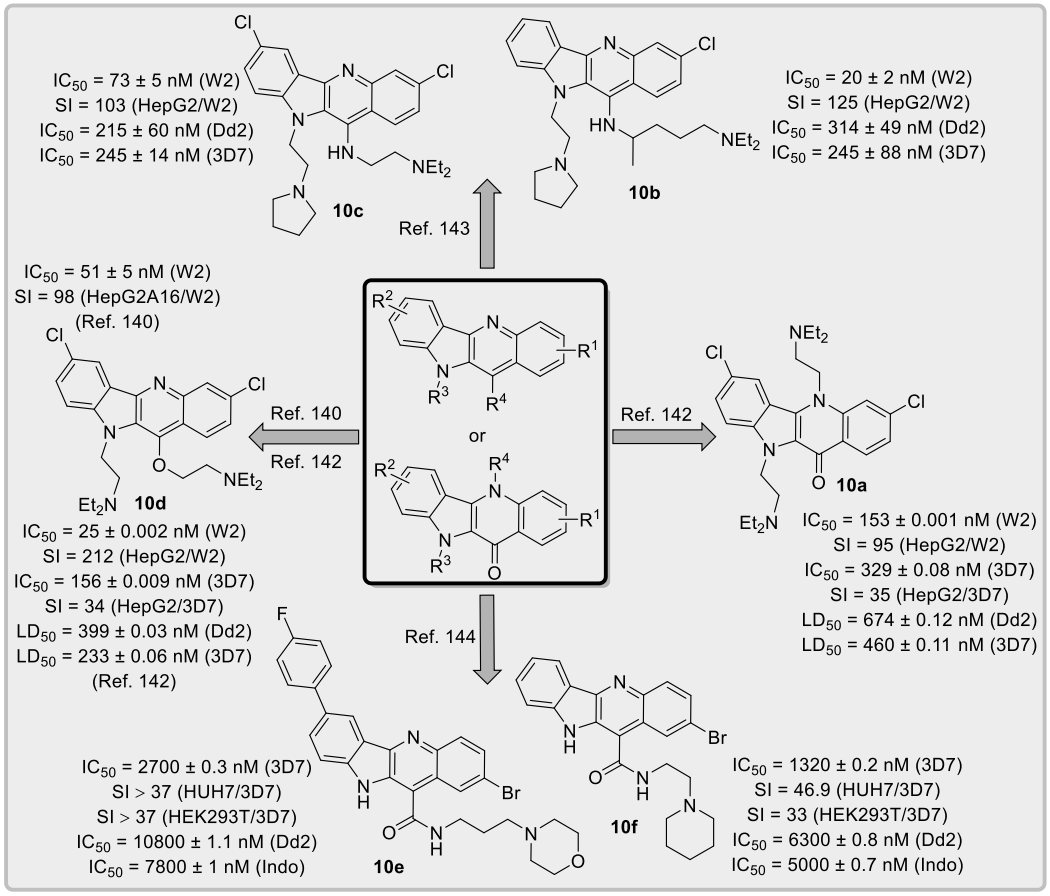

Figure 5: Antimalarial activities of *N*-demethylated cryptolepine (quindoline) analogs.

Bharate and colleagues[144] studied a series of *C*11-carboxamides analogs of indolo[3,2-*b*]quinoline for in vitro antiplasmodial activity against CQ-sensitive 3D7, and CQ-resistant Dd2 and Indo strains of *P. falciparum*. The analogs with halogen at *C*2 and aliphatic amino carboxamide moiety at *C*11 positions showed promising antiplasmodial activity against CQ-sensitive and CQ-resistant strains. Among these analogs, the piperidinylethyl carboxamide analog **10f** and the 2-fluoro-substituted analog **10e** (Figure 5) showed the most potent antiplasmodial activity and good selectivity indices. Mechanistic studies revealed that analog **10f**

targeted the parasite's food vacuole and inhibited the hemoglobin uptake process. The most potent analog, **10f**, also exhibited acceptable oral pharmacokinetic properties and discernible in vivo antimalarial activity in *P. berghei*-infected BALB/c mice. The in vivo studies showed that mice treated with **10f** exhibited a 27-35% suppression of parasitemia from day 7 to day 13. This suppression of parasitemia also resulted in an increased lifespan of the treated mice (average survival time: 27.8 ± 5 days) compared to the untreated control (average survival time: 20.2 ± 2.3 days).

4.2 Neocryptolepine:

Several studies have suggested that neocryptolepine has enormous potential as a viable option for developing new antiplasmodial agents. Unlike other isomeric indoloquinoline alkaloids, such as cryptolepine and isocryptolepine, neocryptolepine has a relatively lower affinity for DNA and topoisomerase II inhibition. In an effort to develop effective and safer malaria treatments by focusing on neocryptolepine, Pieters et al.[117, 145] synthesized several analogs containing different substituents, such as methyl, methoxy, cyano, nitro, and halogen, at the 2-position and evaluated the antiplasmodial activity in vitro against both CQ-sensitive and CQ-resistant *P. falciparum* strains. The results revealed that the synthesized analogs were slightly more potent against the CQ-resistant strain than the CQ-sensitive strain. Notably, 2-methylneocryptolepine **1b** (Figure 6) demonstrated cytotoxicity and antiplasmodial activity similar to cryptolepine. Moreover, the researchers found that the 2-halo-substituted analogs were more active and selective than neocryptolepine. Among these analogs, bromoneocryptolepine **11j** (Figure 6) exhibited the highest selectivity with IC_{50} values of 6.0 and 4.0 μM against CQ-sensitive and CQ-resistant strains *P. falciparum*, respectively, without any apparent cytotoxicity. Although the bromoneocryptolepine **11j** is slightly less active than the cryptolepine, this analog demonstrated a low affinity for DNA and no inhibition of human topoisomerase II. The same group later synthesized 2- or 3-substituted neocryptolepine analogs and tested them for antiplasmodial activity in vitro. In the CQ-sensitive strain, all analogs demonstrated similar effectiveness to neocryptolepine (IC_{50} 27.3 μM), except 2-bromoneocryptolepine **11j** (Figure 6), which was four times more potent (IC_{50} 6.0 μM). For the CQ-resistant strain, all derivatives, except 3-trifluoromethylneocryptolepine, were more effective than neocryptolepine (IC_{50} 14.0 μM), with 2-bromoneocryptolepine **11j** (IC_{50} 4.0 μM) being the most potent. To understand the mechanism of action of these analogs, they performed the β-haematin formation inhibitory assay (detoxification of haem) and the DNA–methyl green displacement assay (interaction with DNA). The results

suggest that these analogs inhibit the β-haematin formation, indicating that inhibition of hemozoin formation plays an important role in their antiplasmodial activity.

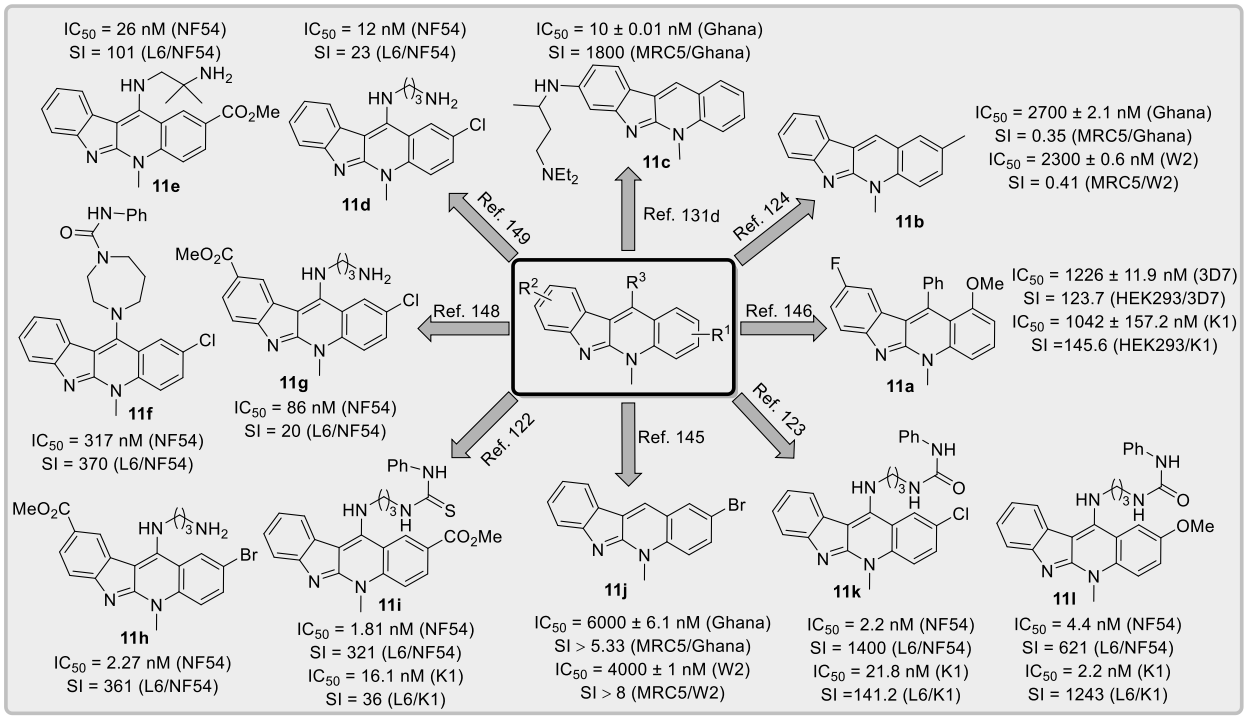

Figure 6: Antimalarial activities of neocryptolepine analogs.

A group led by Ruchirawat[146] has recently evaluated twenty-three neocryptolepine analogs, which contain alkyl, aryl, or halo substituents at various positions for antiplasmodial activity against CQ-sensitive clone 3D7 and CQ-resistant clone K1. Unfortunately, only four compounds yielded positive results in both strains with analog **11a** (Figure 6) demonstrated the best activity and good selectivity.

Augustyns et al.[147] determine the effectiveness of neocryptolepine derivatives with chloro- and aminoalkylamino-substituted structures against a CQ-sensitive *P. falciparum* strain. They found that the mono- and dichlorosubstituted neocryptolepines and norneocryptolepines were less potent than neocryptolepine. However, adding the aminoalkylamino side chain led to a significant increase in antiplasmodial activity. Compound **11c** (Figure 6), an 8-substituted 1,4-diamine derivative, was the most active and selective, with no evidence of cytotoxicity.

Inokuchi's research group[123] conducted extensive studies on the antimalarial properties of neocryptolepine analogs. Their approach involved modifying the aminoalkylamino side chain at *C*11 with different substituents at the *C*2 position. Initially, they introduced 3-aminopropylamino

groups at the *C*11 position and changed the substituents at the *C*2 positions. They found that introducing electron-withdrawing groups (Br, Cl, and CF_3) at the *C*2 position increased the activity against the NF54 compared to the non-substituted analog. Furthermore, the longer chain substituted with the 6-aminohexylamino group at *C*11 showed slightly decreased activity compared to the 3-aminopropylamino. After that, they modified the 3-aminoalkylamino side chain into thiazolidine-4-one, sulfonamides, amide, and urea derivatives and tested for antimalarial activity. The results of this study revealed that the most potent and selective compounds were urea derivatives **11k** and **11l** (Figure 6). In vivo studies showed that the selected analogs were neither potent enough nor toxic to the mice. Another study[122] investigated the antimalarial properties of neocryptolepine analogs against two strains of malaria parasites: NF54 and K1. The researchers modified the neocryptolepine analogs by introducing ester groups at the *C*2 and *C*9 positions and the terminal amino group of the 3-aminopropyl amine substituents at the *C*11 position with a urea/thiourea unit. The results showed that the ester-modified neocryptolepine analogs exhibited higher antiplasmodial activities and good selectivity. Among the tested compounds, **11h** and **11i** (Figure 6) demonstrated the most potent and selective effects. The introduction of an ester group significantly enhanced the effectiveness of these analogs against *P. falciparum* while maintaining low cytotoxicity against normal cells. Moreover, this modification significantly improved the in vivo activity of the neocryptolepine analogs. Later, SAR investigations[148] were carried out on 2,11- and 9,11-disubstituted 6-methylindolo[2,3-*b*]quinolones against the *P. falciparum* CQ-sensitive NF54 strain. The findings revealed that the most effective compounds were **11g** and **11f** (Figure 6), exhibiting IC_{50} values of 86 and 317 nM, respectively. Out of all the tested compounds, **11f** demonstrated high selectivity. Further, the effectiveness of neocryptolepine derivatives was analyzed through SAR studies, which involved modifying the linker between the two nitrogen atoms of the *C*11 aminoalkylamino side chain.[149] Results indicated that linear-side chains with three carbon atom spacers showed superior antiplasmodial activities compared to those with branched carbon atom spacers. Adding a chloro substituent at the *C*2 position, further improved the antiplasmodial activity and selectivity indices. Additionally, the antimalarial activity of ureido and thioureido derivatives was also explored with activity similar to **11d** and **11e** (Figure 6).

4.3 Isocryptolepine:

Compared to cryptolepine and neocryptolepine, relatively fewer SAR studies have been conducted on isocryptolepine. These studies have primarily focused on modifications at the *C*2,

*C*3, *C*6, *C*8, and *C*9 positions of the indolo[3,2-*c*]quinoline core. Go et al.[150] synthesized a small set of 3-chloro-8-methoxy-11H-indolo[3,2-*c*]quinoline analogs by altering the *C*9 position with a basic amino side chain and evaluated in vitro antimalarial activity against a CQ-resistant K1 strain of *P. falciparum*. Compound **12d** (Figure 7), which contains a polar, dibasic piperazinyl moiety at the side chain, was found to be the most active, while compound, which lacks a basic side chain, was the least active. Subsequently, Mak's group[151] also conducted the in vitro activity of *C*9-modified 3-chloro-8-methoxy-11H-indolo[3,2-*c*]quinoline analogs against various isolates of *P. falciparum* and were found to be active against sensitive and resistant isolates of *P. falciparum*. Later, Go and colleagues[152] studied various *N*-substituted piperazinyl methyl analogs of 3-chloro-8-methoxy-11H-indolo[3,2-*c*]quinoline, exploring modifications to their steric bulk and electronic properties. Results showed that analog **12a** (Figure 7), featuring an *N*-ethylpiperazinylmethyl side chain, was the most effective against the K1 strain of *P. falciparum*. The research suggests that activity levels decrease as the size of the dibasic side chain increases. On the other hand, the large charge on the side chain's distal nitrogen (*N*3) is crucial for enhancing activity.

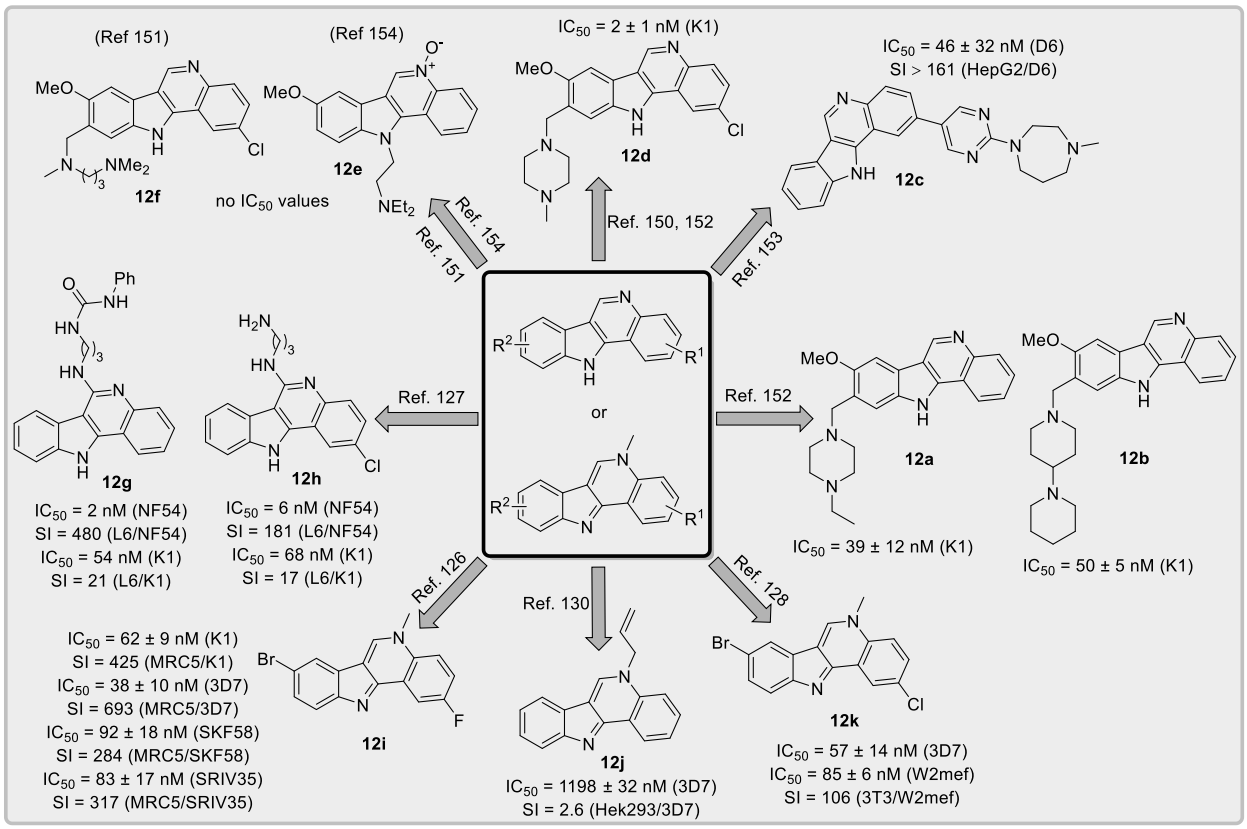

Figure 7: Antimalarial activities of isocryptolepine and *N*-demethylated isocryptolepine analogs

Turner's team[154] synthesized a range of 3-chloroindolo[3,2-*c*]quinoline-5-oxides and evaluated their effectiveness against a typical drug-sensitive strain of *P. berghei*. The compounds were administered to mice in a single subcutaneous dose 72 hours after infection, dissolved or suspended in sesame or peanut oil. Results indicated that the basic side chain and ring *N*-oxide play a critical role in antimalarial activity and that bromine or chlorine in position 3 is essential. Several analogs exhibited promising in vivo antimalarial activity, with analog **12e** (Figure 7) displaying the highest potency.

Inokuchi's team[127] conducted a SAR study on indolo[3,2-*c*]quinolines by modifying substituents at the *C*2, *C*6, and *N*11 positions. In vitro testing was first performed on *C*6-substituted analogs against CQ-sensitive NF54 and CQ-resistant K1 strains with various amine side chains. The analogs that contained ω-aminoalkylamino groups were more effective than those containing alkylamino or benzeneamino groups. After that, the analogs with different substituents at the *C*2 position, namely F, Cl, Br, Me, MeO, and NO_2, were tested. The analog **12h** (Figure 7), which has a 2-chloro substitution, was discovered to exhibit the best activity. Further modification of the side chain amino group led to the discovery of a slightly more potent and selective compound **12g** (Figure 7). Notably, adding *N*11-methyl groups did not contribute to improved activity or selectivity. The analog with the least cytotoxicity was tested in vivo, and on day 4, it showed a 38% decrease in parasitemia.

Murray's team[128] synthesized a small series of mono- and di-substituted analogs of isocryptolepine, which were then tested for in vitro antimalarial activity against both CQ-sensitive 3D7 and CQ-resistant W2mef *P. falciparum* strains. The results were promising, with all analogs demonstrating greater potency than the isocryptolepine. Of the analogs tested, 8-bromo-2-chloroisocryptolepine **12k** (Figure 7) stood out as the most potent and selective. Later, Thongsornkleeb and colleagues[126] synthesized and evaluated a larger series of mono- and di-substituted variants of isocryptolepine to assess their effectiveness against different strains of *P. falciparum* in vitro. The study focused on substituents such as halogen (F, Cl, Br), methyl, and methoxy at various positions of the indoloquinoline core. Several fluorine-substituted analogs showed exceptional selectivity while maintaining good to excellent activities against all four *P. falciparum* strains, with 8-bromo-3-fluoro-isocryptolepine **12i** (Figure 7) being the most effective compound in this series.

4.4 Lipophilic efficiency (LipE) plots:

To study the potential of bioavailability of the indoloquinoline alkaloids (cryptolepine, neocryptolepine, isocryptolepine) and their analogs, we studied the relationship between potency and lipophilicity using the integrated software suite StarDrop by Optibrium. First, we calculated the cLogP and plotted a graph of pEC_{50} vs cLogP, which is referred to as the lipophilic efficiency (LipE) plot (as shown in Figure 8). The LipE plot evaluates the "drug-likeness" of a given compound, and the optimal LipE values for bioavailability range between 5 and 10, with a total range between 1 and 10. We selected *P. falciparum* strains for each indoloquinoline scaffold based on their physicochemical diversity, adequate potency, and appropriate calculated cLogP to indicate the range of LipE (pEC_{50}-cLogP), as shown in Figure 8. Across all the compounds analyzed in this study, we found that analogs bearing amino-alkyl-amino side chain substitutions exhibited a LipE of 4 to 5, as indicated by the red cross. These substitutions improved the potency and reduced lipophilicity of the corresponding parent chemotypes and demonstrated their potential in drug design. Amino-alkyl-amino-alkyl and amino-alkyl-amino-aryl substituents also improved the potency, but in most cases, they significantly decreased cLogP compared to amino-alkyl-amino substituents. This physicochemical trend is best observed in cryptolepine (Figure 8a) and isocryptolepine (Figure 8c). Amino-alkyl-urea-aryl substitutions in neocryptolepine (Figure 8b) showed similar trends. In addition, we observed that mono-halogenated analogs on the indole or quinoline core had lower potency and high cLogP. However, di-halogenation improved potency but had high cLogP. Nevertheless, the cLogP was still much higher for halogenated analogs than amino-alkyl-amino substitutions. We observed this trend across all three chemotypes. Salt of the cryptolepine chemotype improved LipE from 3 to 4, as shown in Figure 8a.

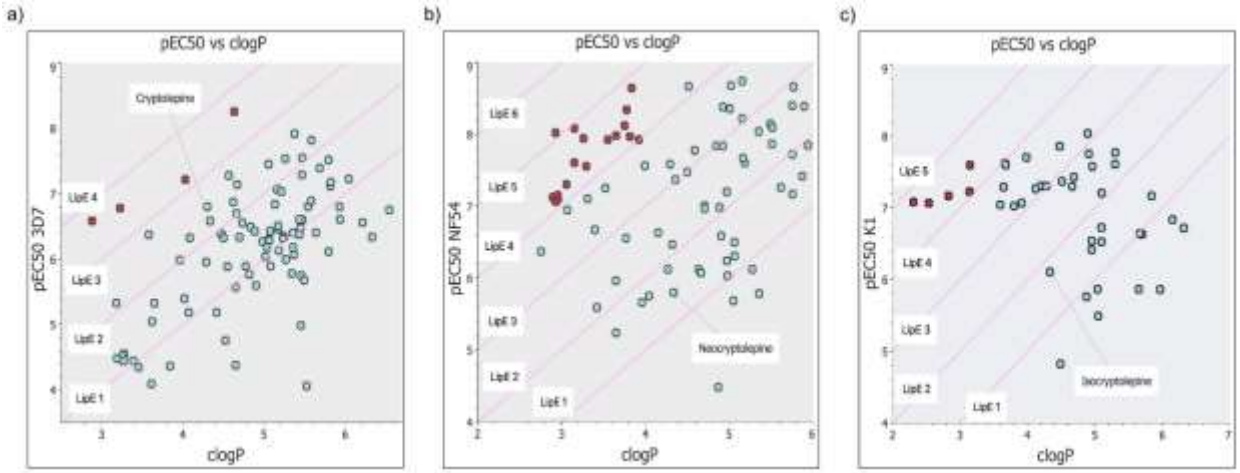

Figure 8: LipE plots of – a) cryptolepine and analogs; b) neocryptolepine and analogs; c) isocryptolepine and analogs.

5. Indoloquinoline-based combination therapy:

Many of the antimalarial drugs currently in use are facing challenges such as drug resistance, poor bioavailability, toxicity, and low water solubility. One well-established and widely used approach to overcome these limitations is combination therapy. This strategy has consistently proven effective in addressing the complexities of malaria treatment. For example, developing hybrid compounds by combining two antimalarial pharmacophores and integrating indoloquinolines into polymer-based carriers demonstrates the success of this approach.[155] By utilizing combination therapy, researchers and pharmaceutical experts continuously innovate to create more effective treatment options for malaria.

In recent years, various studies have been carried out to evaluate the efficacy of indoloquinolines when used in combination with other established antimalarial drugs such as artemisinin derivatives, amodiaquine, lumefantrine, chloroquine, and mefloquine. The primary objective of these studies has been to explore potential synergies between indoloquinolines and the known antimalarial drugs, aiming to develop new and more effective combination therapies to treat malaria.

The Inokuchi group[156] has synthesized a series of hybrid compounds (artesunate–indolo[2,3-*b*]quinoline hybrids, –indolo[3,2-*c*]quinoline hybrid, and –indolo[3,2-b]quinolone hybrids) by coupling the carboxylic acid functionality of artesunate with the amino group of indoloquinolines. These hybrids were tested for their effectiveness against two strains of malaria, CQ-sensitive,

and CQ-resistant, as well as their cytotoxic activities in L6 cells. The results revealed that all the synthesized hybrids are more potent and have less cytotoxicity than their individual, non-hybridized counterparts. The most effective hybrid compound to emerge from this study is **13**, which exhibits IC_{50} values of 0.45 and 0.42 nM against the CQ-sensitive and CQ-resistant strains, respectively, with an RI value of 0.93. At a dosage of 10 mg/kg administered once daily for four days, hybrid compound 13 significantly reduced parasitemia by 89.6% on day 4, extending the mean survival time of mice to 7.7 days.

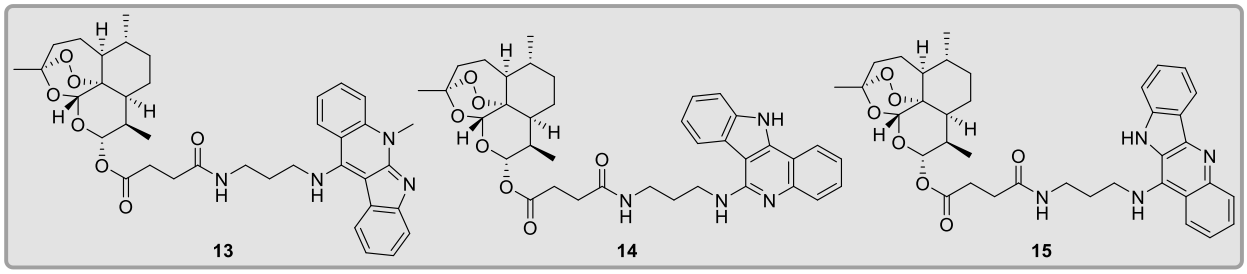

Figure 9: Chemical structures of the artesunate–indoloquinoline hybrids.

Antimalarial activity of cryptolepine in combination with artemisinin derivatives (artemisinin, artemether, and dihydroartemisinin) both in vitro and in vivo was conducted by Ansah et al.[157] Cryptolepine exhibited promising synergistic interactions (a mean ΣFIC50 of less than 0.8) in vitro against *P. falciparum* strain 3D7, with the degree of synergism being more substantial in artemisinin (ΣFIC50 = 0.362), followed by dihydroartemisinin (ΣFIC50 = 0.403) and finally artemether (ΣFIC50 = 0.693). In in vivo antimalarial studies on *P. berghei* NK-65, it was observed that all tested combinations yielded a more significant reduction in parasitemia than the use of cryptolepine or artemether alone on the first day of treatment. This suggests a synergistic effect of the combination of cryptolepine with artemisinin. In all dose levels, the combination of cryptolepine and artemether resulted in a significant suppression rate in the first three days of treatment compared to cryptolepine alone. Additionally, no adverse histopathological, biochemical, or hematological changes were detected in healthy Sprague-Dawley rats, indicating no acute toxicity.

Forkuo and his team[119] conducted a study to explore the effectiveness of cryptolepine when combined with different antimalarial drugs such as amodiaquine, chloroquine, mefloquine, and lumefantrine. The study found that cryptolepine and amodiaquine pairing showed a synergistic effect against the 3D7 *P. falciparum* strain in vitro. The mean ΣFIC50 for this combination was 0.235 ± 0.15. In contrast, the combination of cryptolepine and mefloquine showed an antagonistic effect, with a mean ΣFIC50 of 4.182 ± 0.68. The pairing of cryptolepine with chloroquine or

lumefantrine resulted in an additive effect, with a mean ΣFIC50 of 1.342 ± 0.34 and 1.017 ± 0.45, respectively.

Al-Kassas and co-workers[158, 159] developed a gelatin nanoformulation loaded with cryptolepine hydrochloride to improve the compound's pharmacokinetics and chemo-suppressive activity in vivo. The primary goals of any formulation strategy are to effectively deliver bioactive compounds while ensuring safety, acceptability, ease of administration, stability, and affordability. Formulations that achieve targeted delivery to affected tissues and cells limit systemic distribution, avoid uptake by the reticuloendothelial system, and provide sustained release can significantly enhance the efficacy and safety of bioactive compounds. The in vivo results for cryptolepine hydrochloride and its gelatin nanoparticles have shown promising pharmacokinetics and schizonticidal activity.[158, 159] The compound is well-tolerated, with no observable acute toxicity. Cryptolepine hydrochloride exhibits a long plasma half-life when administered in nanoparticulate form, enabling once-a-day dosing. The reduced distribution rate of the cryptolepine hydrochloride-loaded gelatin nanoparticles (CHN) injection is crucial for the formulation's safety and effectiveness as an antimalarial agent. CHN has shown more significant chemo-suppressive activity than cryptolepine hydrochloride solution (CHS) on a dose-to-dose basis. This difference could be attributed to the pharmacokinetic profiles of the two dosage forms, suggesting that CHN delivers higher plasma drug levels, reduced distribution rate, reduced clearance, and extended half-life, all of which may enhance the delivery of the active compound to blood parasites.

6. Summary and Outlook:

Nature has provided several drugs and drug leads for treating infectious and non-infectious diseases, including malaria and cancer. Malaria is a highly infectious disease that is transmitted through mosquitoes and is a significant public health concern in as many as 85 countries, especially in Africa. For several decades, the roots of *C. sanguinolenta* have been used in Central and West Africa to treat malaria and fever. Chemical analysis has revealed that this plant is rich in indoloquinoline alkaloids, demonstrating a remarkable capability to combat malaria. The extract of *C. sanguinolenta* and the indoloquinoline alkaloids isolated from this plant, particularly cryptolepine, neocryptolepine, and isocryptolepine, have shown strong in vitro and in vivo antimalarial properties against various strains of *P. falciparum*. The antimalarial activity of these alkaloids is primarily attributed to the combination of non-selective DNA interaction and the inhibition of hemozoin formation. Several studies have demonstrated that indoloquinoline possesses a crucial framework for developing antimalarial drugs. This review focused on the

antimalarial activities of three indoloquinolines - cryptolepine, neocryptolepine, and isocryptolepine. The various studies suggest that cryptolepine is the most potent among the three compounds, while neocryptolepine emerges as the most selective. The study provides valuable insights into the properties and potential applications of these indoloquinolines for developing new antimalarial therapies. The simple chemical structure of indoloquinoline, along with its ability to incorporate chemical diversity, allows for the design and synthesis of analogs with better activity and selectivity profile. In recent decades, hundreds of indoloquinolines have been synthesized, revealing structure-activity relationships and providing insights into the mechanisms of action of this class of tetracyclic indoloquinolines. The following general trends were observed from SAR studies of these three indoloquinolines:

1) the analogs containing two halogen atoms exhibited improved potency and selectivity.

2) the analogs that had been *N*-demethylated lost their potency.

3) the analogs with basic side chains, such as aminoalkyl, alkylamino, or aminoalkylamino, positively impacted the potency and selectivity of these indoloquinolines. These groups also significantly improve the absorption, distribution, metabolism, and excretion (ADME) properties of the indoloquinolines, thereby increasing bioavailability.

4) various studies support that indoloquinolines' antimalarial activity results from the combination of two mechanisms: selective inhibition of the heme detoxification process and non-selective DNA interaction.

5) the LipE plot and cLogP analysis of the cryptolepine, neocryptolepine, isocryptolepine, and their analogs indicate that the synthesized compounds lack drug-like properties.

6) the combination of indoloquinolines with other antimalarial drugs has exhibited encouraging synergistic effects. In light of these findings, indoloquinolines have the potential to serve as a valuable scaffold for the development of antimalarial agents.

Despite significant efforts to modify indoloquinolines structurally, none of the candidates have progressed to human clinical trials. Some challenges that need to be addressed in future work are:

1) developing additional analogs with optimal pharmacokinetic properties, improved lipophilic index, minimal toxicity, and cost-effectiveness is crucial in addressing key challenges in the field, including clinical translation and potential scalability.

2) conventional organic synthesis methods are often deemed incompatible with environmental sustainability. Considering the predominantly impoverished status of malaria patients, the accessibility of antimalarial medications holds paramount importance. A viable strategy to tackle these challenges involves the cultivation of *C. sanguinolenta* and the extraction of

indoloquinolines from its roots as a foundation for the production of semi-synthetic analogs, which can serve as precursors for the development of innovative antimalarial drugs.

3) understand the detailed mechanism of action by which the tetracyclic indoloquinoline framework is involved in antiplasmodial activity. While it is believed that the indoloquinoline framework may work by inhibiting the formation of β-hematin or intercalating with DNA, more research is necessary to confirm these mechanisms.

4) identify the specific intramolecular interactions between the indoloquinolines and their biomolecular targets. A detailed map of intermolecular interactions will enable medicinal chemists to design indoloquinolines with improved binding to the biomolecular targets associated with antiplasmodial activity while reducing the binding to the unwanted toxicity targets, improving the selectivity. Therefore, further research is needed to identify these targets.

In general, to fully uncover the potential therapeutic applications of indoloquinoline alkaloids, a deeper investigation into their structure-activity relationships and the underlying mechanisms responsible for their effects is imperative. This includes exploring biosynthesis, signaling pathways, and potential interconnections, opening new avenues for discovering and advancing the field.

7. Abbreviations: WHO – World Health Organization; *P.* – *Plasmodium*; FDA – Food and Drug Administration; ACTs – Artimisinin-based combination therapies; ATM – African traditional medicine; *C.* – *Cryptolepis*; CQ – Chloroquine; DNA – Deoxyribonucleic acid; PPA – Polyphosphoric acid; DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; PivOH – Pivalic acid; TBHP – *tert*-Butyl hydroperoxide; TfOH – Triflic acid; SI – Selectivity index; SAR – Structure-activity relationship; giRI – Growth inhibition resistance indices; RI – Resistance index.

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