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NEW POTENTIAL ANTIMALARIAL AGENTS: SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SCHIFF BASE LIGAND AS ANTIMALARIAL AGENTS

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ABSTRACT: Plasmodium falciparum is the protozoan parasite responsible for the majority of life-threatening cases of human malaria, causing more than one million deaths a year. The global emergence of drug-resistant malarial parasites necessitates identification and characterization of novel drug targets. At present, α-carbonic anhydrase (CA) genes are identified in limited numbers of parasites in both protozoa and helminthes, however, the malarial genes are found in four species of Plasmodium. The CA gene of P. falciparum encodes an α- carbonic anhydrase enzyme possessing catalytic properties distinct of that of the human host CA I and II isozymes. P. falciparum native and recombinant enzymes have been prepared. Eighteen new schiff base ligand **(AA01-AA18)** related to previously reported potent blood schizontocidal antimalarial agent, 2-tertbutylprimaquine were synthesized and evaluated for *in vivo* antimalarial activities against drug-sensitive *Plasmodium falciparum* strain. Acute toxicity studies found that synthesized compounds were less toxic than the parent compound chloroquine, while preserving the desired antimalarial activity. Five of the analogues (**AA3, AA6, AA-4, AA-9 and A-10**) have exhibited curative antimalarial activity at a dose of 25mg/kg/day×4 and produced suppressive activity at a lower dose of 10 mg/kg/day×4The results of antimalarial activity showed that the ligand AA-**1** exhibits moderately active while complex AA-**6** exhibits good activity for chloroquine sensitive and resistant.

INTRODUCTION: Malaria is the most serious, complex and refractory health problems facing humanity. Almost one half of the world's population is exposed to the threat of malaria and the disease is responsible for two million deaths each year, either directly or in association with acute respiratory infections and anaemia and upto 1 million of those deaths are children.

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Malaria is a leading cause of morbidity and mortality in developing world [1]. Chloroquine was a mainstream drug in the fight against *Plasmodium falciparum*, but its efficacy is being eroded by the emergence of resistant parasites.

The spread of chloroquine resistance has prompted the re-investigation of the chemistry and pharmacology of alternative antimalarials such as amodiaquine, other 4- aminoquinoline which proved to be effective against chloroquine-resistant strains [2, 3].

Amodiaquine is a 4-aminoquinoline antimalarial which is effective against many chloroquine resistant strains of *P. falciparum*.

However, clinical use of amodiaquine has been severely restricted because of associations with hepatotoxicity and agranulocytosis [4, 5]. It has been suggested that the toxicity of amodiaquine is related to the reactive electrophillic metabolites formed by oxidation of its phenolic side chain, especially to the formation of a quinineimine by cytochrome P-450- catalyzed biological oxidation (**Scheme 1**).

It has been found that amodiaquine is excreted in bile exclusively as the 5´ thioether conjugates (glutathione and cysteinyl) in rats [6]. This observation indicates that the parent drug undergoes extensive bioactivation *in vivo* to form amodiaquine quinoneimine (AQQI) or semi quinoneimine (AQSQI) with subsequent conjugation of glutathione [7].

The enzyme which catalyzes the formation of ammonia and carbon dioxide by hydrolysis of urea is a nickel based metalloenzyme, is commonly known as urease enzyme [10]. A large variety of prokaryote, most of the plants and a fewer fungi possess this enzyme [11]. There are various negative implications caused by elevation of pH due to high concentration of ammonia produced by such type of reactions, in agriculture and medicine [12]. Such type of negative implications can be minimized by decreasing the activity of urease enzyme by employing suitable inhibitors. Inhibitors of urease can be broadly classified into two categories:

(i) Active site directed (substrate-like),

(ii) Mechanism-based directed.

The urease due to its high substrate (urea) specificity can only bind to a few inhibitors with a similar binding mode as urea.

The oxidative stress associated with various important diseases and pathogens are controlled by ROS reactive oxygen species which include superoxide anions, hydrogen peroxide, hydroxyl and nitric oxide radicals [13]. The damages caused by free radicals are protected by antimalarial, the radical mediated toxicity and as a result these antimalarials serve as major defense. The prevention and treatment of complicated diseases such as atherosclerosis, stroke, cancer and diabetes is carried out by employing antimalarial agents [14].

Ever since the discovery of the first case of chloroquine resistance along the Thai-Cambodian border in the late 1950s, Southeast Asia has played an important role as a focus for the development of drug resistance in *Plasmodium falciparum.* Although the first case of quinine resistance had been reported much earlier from South America, the onset of chloroquine resistance marked the beginning of a new chapter in the history of malaria in Southeast Asia and by 1973 chloroquine finally had to be replaced by the combination of sulphadoxine and pyrimethamine (SP) as first line drug for the treatment of uncomplicated malaria in Thailand and more than 10 African countries have also switched their first line drug to SP. In 1985, eventually SP was replaced by mefloquine. The rapid development of resistance to this new drug leads to the introduction of artemisinin as a combination drug in the mid-1990s.

The above grounds prompted us to work and report the synthesis and characterization of nickel (II) complex **2** of the Schiff base ligand **1** conduct biological evaluation.

EXPERIMENTAL [36]:

1. **Materials and methods:** The chemicals and reagents purchased from Merck were used without any alteration. The hydrated metal salt was utilized like hydrated metal (II) acetate [$Ni(CH_3COO)_2.4H_2O$]. The use of thoroughly washed and oven dried glassware was made sure during the whole work.

2. **Physical measurements:** The process of weighing was accomplished by using electric Mettler Toledo balance, of AL 204 model. The melting points reported are uncorrected and were taken by using melting point apparatus of Gallenkamp. Perkin-Elmer 4400 Series II elemental analyzer was employed for elemental analysis. Jasco 300 FT-IR spectrometer with a range of 400-4000 cm^{-1} was employed for taking IR spectra of the compounds. The conductivity meter with model Jenway 4010 was used for the measurement molar conductance of compounds. The UV spectra of compounds for studying electronic transitions were taken by using Specord 200 UV-Vis spectrophotometer. The recording of El-MS spectra was conducted

by electron impact mode on Finnigan MAT-112 spectrometer (Finnigan, Waltham, MA, USA) and m/z (%) of $[M]^+$ ions reported. The compounds were subjected to TLC on precoated silica gel G-25-UV254 plates (E-Merck). The recording of ^{1}H-NMR spectra of compounds in DMSO-d_6 was made on a Bruker AMX-300 spectrometer. For this purpose, chemical shift vlues (δ) are reported in ppm, based on the internal standard *i.e.*, tetramethylsilane and *J* values (*i.e*., scalar coupling constant) are shown in Hertz.

Single-crystal X-ray diffraction data was collected on Bruker Smart APEX II, CCD 4-K area detector diffractometer [17]. Data reductions were performed by using SAINT program. The structure was solved by direct method [18] and refined by full-matrix least squares on F^2 by using the SHELXTL-PC package [19]. The figures were plotted with the aid of ORTEP program [20].

3. **Synthesis of Schiff base ligand:** The addition of 3-4 drops of conc. H_2SO_4 to a mixture of ethylenediamine (0.01 mol in 60 mL MeOH) and salicylaldehyde (0.02 mole in 60 mL MeOH) was carried out and it was refluxed in water bath for 4 hours at 70^{o}C and then it was kept for cooling in refrigerator. *n*-hexane was used for washing these yellow flakes and recrystallization in absolute methanol was accomplished. Desicator containing P_2O_5 was used for drying purpose.

4. **2-{[(2-{[(E)-(2-hydroxyphenyl)methylidene] amino}ethyl)imino]methyl}phenol 1:** The compound **1** was obtained with 91.03% yield as yellow flakes. m.p: 126 ºC; IR (KBr, ν_{max} cm^{-1}): 3471 (O-H), 3224 (C=N---H-O), 2932 (C-H), 1618 (C=N), 1491 (C=C); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.34 (s, -OH), 8.58 (2H, s, H-5, -7), 7.40 (2H, dd, *J* = 7.6, 1.6 Hz, H-9, -18), 7.30 (2H, ddd, *J* = 8.8, 7.6, 1.6 Hz, H-11, -16), 6.85 (4H, m, H-10, -12, -15, -17), 3.91 (4H, s, H-1, -2); EI-MS: *m/z* (%) 268.1 $[M]^+$ (calcd. 268.1 for $C_{16}H_{16}N_2O_2$); Elemental analysis: found (calcd. %); C: 66.84 (71.62), H: 6.87 (6.01), N: 11.63 (10.44).

5. **Synthesis of Ni^{2+} Complex:** 0.01 mole of nickel (II) acetate was added slowly with continuous stirring to the Schiff base ligand **1** (0.01 mole, 100 mL) in equimolar ratio and mixture was then refluxed for 45 minutes. A solution of 1M NaOH was added in dropwise manner and pH was gradually raised to a suitable pH value for complex formation. Maroon coloured crystals were obtained by reluxing the reaction mixture for 90 minutes under vacuum. It was concentrated in a way that the volume of reaction mixture reduced to half of its original volume. The product thus obtained was washed with cooled methanol after filteration. Absolute methanol was used for recrystallization.

6. **2-{[(2-{[(E)-(2-hydroxyphenyl)methylidene] amino}ethyl)imino]methyl}phenol-nickel (II) 2:** The percentage yield of complex **2** was 89.31% yield. in the form of maroon coloured crystals m.p: 203 ºC; IR (KBr, ν_{max} cm^{-1}): 2933 (C-H), 1524 (C=N), 1435 (C=C), 590 (Ni-N), 465 (Ni-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.88 (2H, s, H-5, -7), 7.24 (2H, d, J = 7.2 Hz, H-9, -18), 7.16 (2H, t, J = 7.2 Hz, H-11, -16), 6.69 (2H, d, J = 8.4 Hz, H-12, -15), 6.50 (2H, t, J = 7.2 Hz, H-10, -17), 3.41 (4H, s, H-1, -2); EI-MS: *m/z* (%) 324.0 $[M]^+$ (calcd. 324.0 for $C_{16}H_{14}N_2O_2Ni$); Elemental analysis: Found (calcd. %); 57.00 (59.13), H: 3.80 (4.34), N: 10.95 (8.62), Ni: 18.13 (18.06).

7. **Biological studies:** Ferheen *et al* methodology was adopted for carrying out antimalarial (DPPH scavenging) and chloroquine sensitive strain and resistance strain of these compounds, however a modified method reported by Bibi *et al* was employed for the measurement of diameter of zone of inhibition for antimalarial assay and then calculation of % inhibition was carried out [21].

RESULTS AND DISCUSSION

Synthesis and characterization: Salicylaldehyde upon reaction with ethylenediamine resulted in the formation of Schiff base ligand **1**; however it was resulted in the formation of a complex **2** upon treatment with Ni (II) acetate. A very much clear evidence about the stability of complex **2** was determined by the fact that this compound possesses a high melting point *i.e.* 203^{o}C.

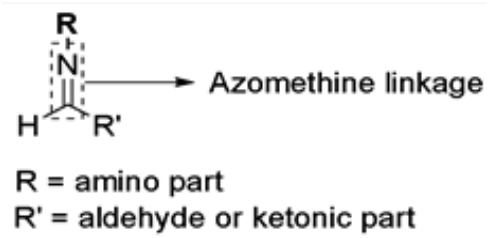


FIGURE 1: GENERAL REPRESENTATION OF THE STRUCTURE OF A SCHIFF BASE

^{1}H-NMR spectra: The presence of a hydrogen atom at δ 8.58 (2H, s) in ^{1}H-NMR spectrum indicated the presence of azomethine proton in ligand **1** and strengthened the idea that product contains azomethine linkage. The chemical shift of these hydrogens underwent a shift towards downfield region *i.e.* δ 7.88 (2H, s) and signals for two hydrogens at *δ* 13.34(s) in ligand **1** disappeared from the spectrum of complex **2** which confirmed that oxygen atoms are involved in coordination.

Infrared spectra: The involvement of azomethine group in complex formation was determined by observing IR spectra of the complex **2** which showed shift in the position of a band at 1618 cm^{-1} due to the presence of ν(-C=N-) (azomethine) in ligand towards lower frequency region *i.e.* 1530 cm^{-1} in the spectrum of complex **2** [22]. The disappearance of distinguishing bands of carbonyl group ν(C=O) group and the amino group indicated the completion of condensation reaction.

The presence of a band at 3224 cm^{-1} for the ligand **1** in IR spectrum confirmed the presence of intramolecular hydrogen bonding. The bands at 590 and 465 cm^{-1} were assigned to the vibrations of (Ni-N) and (Ni-O) [23] respectively, in IR spectrum which is the direct evidence for involvement of heteroatoms (*i.e.* oxygen and nitrogen) of ligand in the coordination.

EI-MS spectra and microanalysis: The examination of stoichiometric composition of ligand AA-**1** and its complex AA- **2** was made by recording and comparing EI-MS spectra of ligand AA-**1** and complex AA-**2**. The ligand AA-**1** showed molecular ion peak [M]$^+$ at m/z 268.1 and the complex AA-**2** on the other hand was observed at m/z 324.0 which confirmed 1:1 ratio of metal and ligand in the complex. The data of EI-MS data was found in concurrence with the data of microanalysis.

Molar conductance: The non-electrolytic nature of complex was suggested by the molar conductance (λm) of complex which was measured in dimethyl formamide (10^{-3} M) and was found 6.21 ohm^{-1} cm^2 mol^{-1}.

Electronic spectra and magnetic moment: The π – π* transition of the azomethine (>C=N–) chromophore in ligand was observed at 329 nm in UV/Vis spectrum. The involvement of azomethine nitrogen in coordination/ complexation was also supported by the shift of azomethine band towards longer wavelength in the spectrum of complex **2**. The appearance of bands at 381, 461 and 492 nm in UV/Vis spectrum of complex was observed and these bands were assigned to $^1A_1g \rightarrow {}^1A_2g$, $^1A_1g \rightarrow {}^1B_1g$ and $^1A_1g \rightarrow {}^1E_1g$ transitions which confirmed that geometry of the complex **2** is square planar[24]. 2.01 B.M. was the observed value for magnetic moment of complex and is in full concurrence with the literature reported data [25].

Single-crystal X-Ray diffraction analysis: It was carried out to establish the structure of complex **2** (**Scheme 1**). The ORTEP diagrams of complex **2** (**Figure 2**) showed that mononuclear nickel (II) complex, [Ni($C_{16}H_{14}N_2O_2$)], the Ni atom is coordinated with four donor atoms of the Schiff base ligand to adopt square-planar geometry. The two benzene rings are each planner with the dihedral angle of 6.61(13).

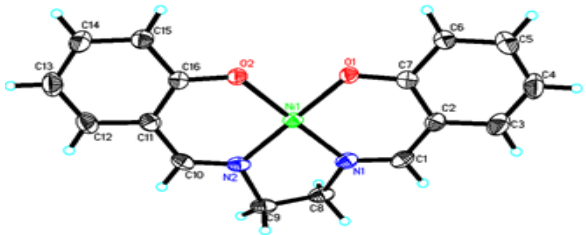
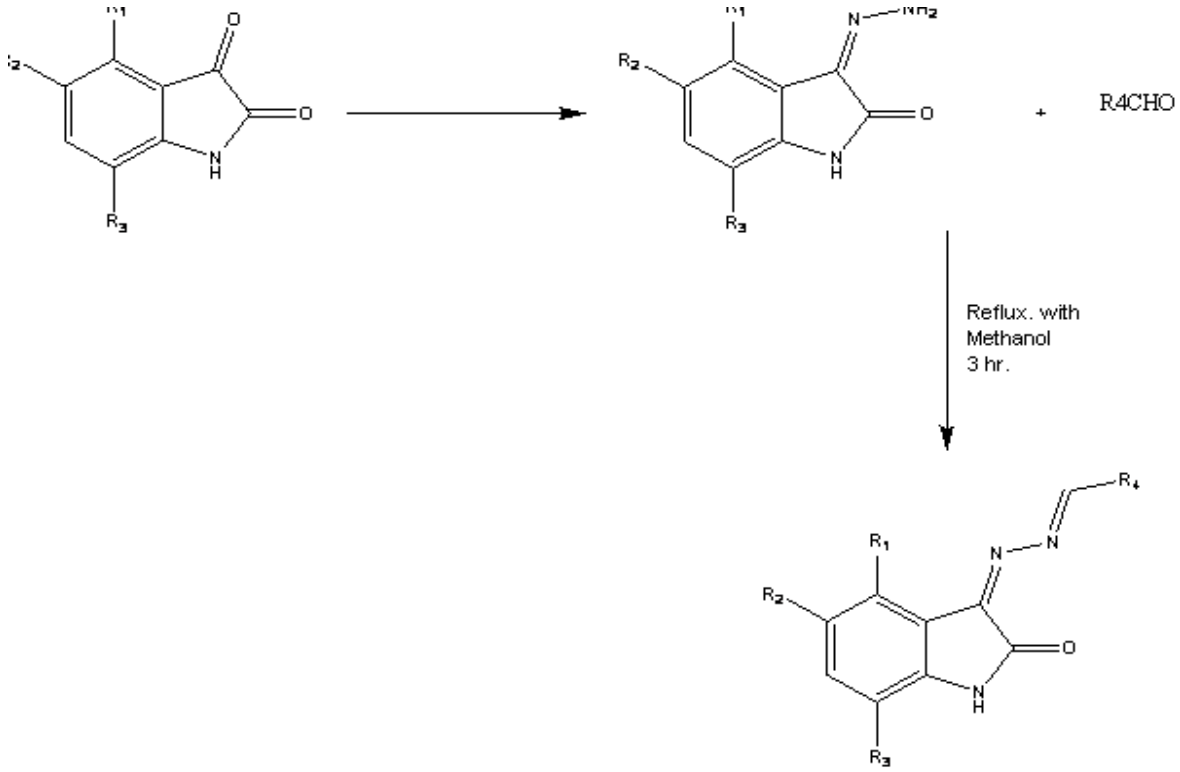
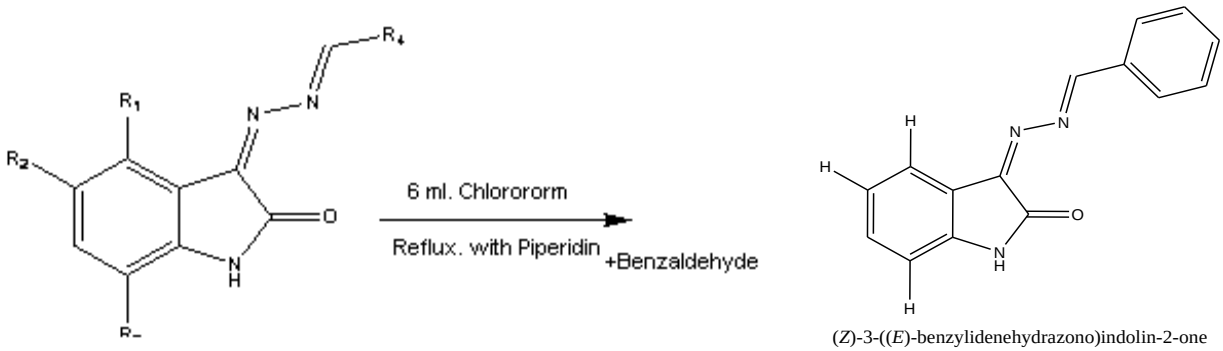


FIGURE 2: SYNTHESIS OF SCHIFF BASE LIGAND AA-1 AND ITS Ni (II) COMPLEX AA-2

The five member ring adopts an envelope conformation with maximum deviation of 0.156(2) for N1 atom from the atom from the least square plane. The bond lengths and angles are similar to those in other structurally related compounds [26]. In the crystal structure, the H atoms of C_8 and C_9 are involved in hydrogen bonding with atoms O_1 and O_2 of a neighbouring molecule *via* C_8---H_{8B}---O_2 and C_9---H_{9A}---O_2 intermolecular interactions and lead to the formation of chain running parallel along the *c* axis (**Figure 3**).



SCHEME 1



(*Z*)-3-((*E*)-benzylidenehydrazono)indolin-2-one

SCHEME 2

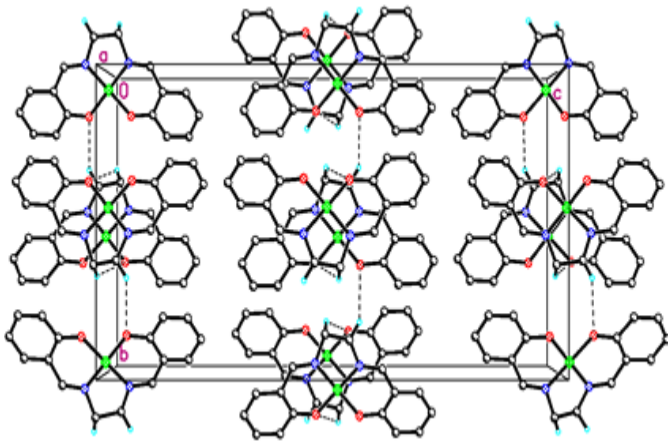


FIGURE 3: ORTEP DIAGRAM OF Ni (II) COMPLEX 2

Crystal data of complex **2:** $Ni(C_{16}H_{14}N_2O_2)$, Mr = 325.00, Orthorhombic, space group *Pbca*, *a* = 7.4785(4) Å , *b* = 13.8271(7) Å, *c* = 26.1344(14) Å, *V* = 2702.5(2)Å ^{3}, *Z* = 8, ρ_{calc} = 1.598 mg/m^3, *F*(000) = 1344, μ(Mo Kα = 0.71073 Å, max/min transmission 0.8935/0.6105 crystal dimensions 0.38 x 0.28 x 0.08, 0.70◦ < θ< 25.5◦, 14710 reflections were collected, of which 2506 reflections were observed (R_{int} = 0.0387).

The *R* values were: R_1 = 0.0318, wR_2 = 0.0763 for I > 2σ(I), and R_1 = 0.0464, wR_2 = 0.0853 for all data; max/min residual electron density: 0.527/-0.226 e A$^{\circ -3}$.

Suggested structural formula of the complex 2: It has been established by the foregoing discussion that nitrogen atoms of imino group and oxygen atoms of Schiff base ligand are involved in complexation. Scheme 1 illustrates the tentative proposed structure for complex **2**.

Biological studies [37-39]: The urease inhibition and antimalarial activities of complex **2** and Schiff base ligand AA-**1** were conducted by screening these compounds.

The reason for the non-significant antimalarial ability of the compounds **1-2** can be explained by looking into the structures of these compounds. It is well known that the compounds with structures containing one or more functional groups such as –OH, –SH, –COOH, –N, –S–, –O– can show antimalarial activity (**Figure 4**). But in Schiff base ligand **1**, hydroxyls are involved in hydrogen bonding and in case of complex AA-**2**; these are utilized in complex formation. That is why; the compounds have non-significant antimalarial activity.

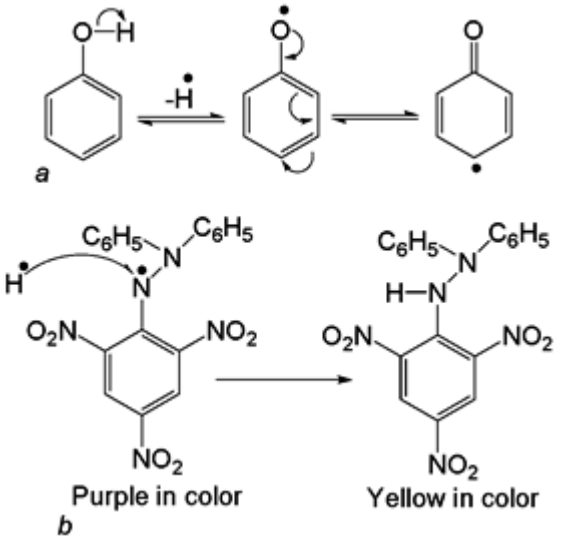


FIGURE 4: PACKING OF THE Ni (II) COMPLEX 2. Intermolecular C—H···O hydrogen bonds are shown as dashed lines

1. The *P. falciparum* F-32-Tanzania chloroquine-sensitive strain, FcM29 and FcB1-Columbia chloroquine-resistant strains were cultured according to Trager and Jensen [25], with modifications [26]. The cultures were synchronized by a combination of magnetic concentration and 5% D-sorbitol lysis (Merck, Darmstadt, Germany) [27, 28]. The F-32-Tanzania strain was considered to be chloroquine-sensitive (chloroquine IC_{50}: 38 ± 6 nM); the FcM29 and FcB1-Columbia strains were considered to be chloroquine-resistant (chloroquine IC_{50}: 170 ± 32 nM and 230 ± 11 nM, 196 ± 31 nM, and > 100 nM, respectively). Anti-plasmodial activity was determined by the [^{3}H]-hypoxanthine (Amersham-France) incorporation method [29]. The resistance index was calculated as follows: IC_{50} F32/IC_{50} FcB1 and IC_{50} F32/IC_{50} FcM29.

The sensitivity of different stages of *P. falciparum* was tested using the FcB1 strain. Serial dilutions of nitidine, which were close to its IC_{50} determined previously on this strain, were prepared. After synchronization over a six-hour period (time between magnetic collection of previous stages and sorbitol lysis after invasion), the parasites were plated at ring stage in 24-well plates. The drugs (nitidine and chloroquine as a control) were added, and the plates were incubated for 8 h; the corresponding wells were then washed while the drugs were added into the new wells for eight-hour incubation. The cultures were then incubated until the end of the erythrocytic cycle plus additional 24 h. Giemsa-stained thin smears were made, and parasitaemia was confirmed by the numeration of at least 10,000 erythrocytes [30].

In vitro antimalarial effects of the investigated compounds were tested against activity against chloroquine sensitive strain and resistance strain. The results showed that the AA-5 exhibits moderate activity, but complex AA-**10** exhibits good activity for chloroquine sensitive strain and resistance strain species and significant for Gram-negative species (**Table 1**).

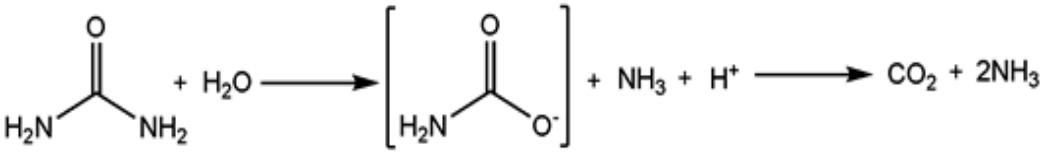


FIGURE 5(A): REMOVAL OF A HYDROGEN ATOM FROM THE COMPOUND. 5(B): HYDROGEN ATOM DONATED TO DPPH RADICAL BY COMPOUND

TABLE 1: ANTIMALARIA AND CHLOROQUINE SENSITIVE STRAIN AND RESISTANCE STRAIN OF SCHIFF BASE LIGAND AA-1 - AA-18

Compound Code	IC50 ^{3D7} (AACSS)	IC80^{3D7} (AACSS)	IC50^{W} (AACRS)
AA-1	22.1	50.6	32.8
AA-2	>50	ND	ND
AA-3	16.3	42.3	51.1
AA-4	3.6	12.3	18.3
AA-5	2.1	6	2
AA-6	4.3	8	10
AA-7	10.2	19.3	25.2
AA-8	19.6	ND	ND
AA-9	>50	ND	ND
AA-10	4.1	12	18
AA-11	15.6	ND	ND
AA-12	10.2	ND	ND
AA-13	19.3	ND	19
AA-14	15.2	ND	16
AA-15	14.0	ND	25
AA-16	7.3	ND	18
AA-17	10.1	46	12
AA-18	17.1	19	15

AACSS - activity against chloroquine sensitive strain; AACRS - activity against chloroquine resistance strain

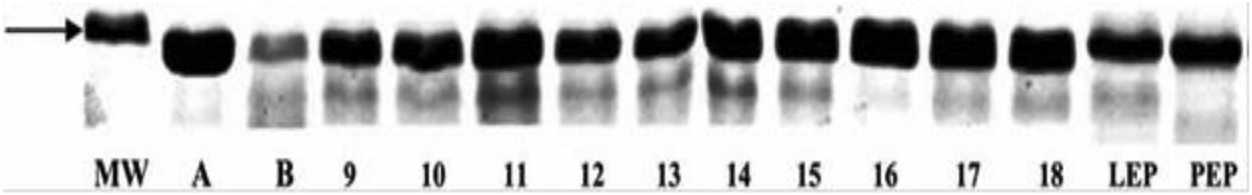


FIGURE 6: EFFECTS ON GLOBIN HYDROLYSIS OF QUINOLINYLMETHYLIDENE-5, 7-DIMETHOXY-INDANONE DERIVATIVES. The samples were solubilized in SDS-sample buffer containing β-mercaptoethanol and boiled before electrophoresis in 15 % SDS-PAGE gels. The gels were stained with Coomassie blue. The position of molecular weight (MW) standard is shown in kilodaltons (kDa). Undegraded globin appears at 14,4 kDa; A: control hemoglobin, without enzyme; B: control, enzyme with hemoglobin; **9-18**: compounds (100 μM); LEP: leupeptin (100 μM); PEP: pepstatin (100 μM).

CONCLUSIONS: On the basis of this work, it is concluded that Schiff base ligand **AA-5** and its complex **AA-10** are non-significant as compared to standard BHA and Schiff base AA-5 has significant result while the complex AA-**5** shows non-significant urease inhibition as compared with thiourea. *In vitro* antimalarial effects of the investigated compounds showed that the ligand AA-**10** exhibits moderate activity, but complex **AA-5 and AA-10** exhibits good activity for chloroquine sensitive strain and resistance strainspecies and significant for Gram-negative species

Supplementary material: All spectral and structural data was published in International Journal of Biomedical Research [36].

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