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Der Pharma Chemica, 2010, 2(4): 271-277
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Synthesis, characterization and antimalarial screening of some new *N*-[(2-chloroquinolin-3-yl)methylene]benzenamines

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ABSTRACT

A convenient synthesis of N-[(2-chloroquinolin-3-yl)methylene]benzenamines (1-12) (Schiff's bases), is achieved in two steps. Acetanilide on reaction Vilsmeier-Haack reagent give 2-chloro-3-formyl quinoline followed by reaction with different substituted aryl amines. All the compounds have been characterized by their melting point, elemental analysis, IR, ^{1}H NMR & MASS spectra. The synthesized compounds have been screened for antimalarial activity.

Keywords: Vilsmeier-Haack reaction, 2-Chloro-3-formyl quinoline, *N*-[(2-chloroquinolin-3-yl)methylene]benzenamines, Schiff's base, Antimalarial screening

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INTRODUCTION

Malaria is caused by Plasmodium infection, transmitted by the female anopheles mosquitoes. Each year, there are approximately 350 million to 500 million cases of malaria, killing between one million and three million people [1]. Malaria remains one of the most dreaded diseases of the developing world. To combat malaria, new drugs are desperately needed, but traditional mechanisms for drug development have provided few drugs to treat diseases of the developing world [2]. Despite continuous research efforts of more than two decades, we are unable to have control of malaria. Treatment of malaria is becoming more difficult due to the resistance of the parasite to standard antimalarial drugs, in particular to chloroquine, which had been the affordable and effective antimalarial mainstay for more than 50 years [3,4] to the resistance of mosquitoes to insecticides, and due to climatic changes that have enlarged areas of disease transmission.

Quinoline and its derivatives have wide applications as drugs and pharmaceuticals and widely used as antimalarial drugs [5-10]. Therefore, considerable efforts have been directed towards the preparation and synthetic manipulation of quinolines and a number of compounds have been obtained with antimalarial activity.

MATERIALS AND METHODS

All the melting points were taken in open capillary tube and expressed in ºC. The purity of all the synthesized compounds was checked by TLC. TLC aluminum sheet silica gel 60 F_{254} (Merck) was used in TLC analysis. IR spectra were recorded on a SHIMADZU 8400 S spectrophotometer using KBr technique and ^{1}H NMR spectra on a Brucker DRX 300 in DMSO-d_6 as a solvent at 300 MHz using TMS as an internal standard. Chemical shifts are expressed relative to residual DMSO in parts per million (ppm). Mass spectrum was recorded on a LC-MS (Shimadzu-2010 AT, software class VP). Elemental analysis was carried out on Elemental Vario EL III Carlo Erba 1108. Chemical reagents were obtained from S D Fine Chem Limited, Mumbai and Qualigens Fine Chemicals, Mumbai of analytical grade. All the solvents were distilled and dried with the usual desiccant.

***N*-[(2-Chloroquinolin-3-yl)methylene]benzenamine, 1:** IR (KBr) ν: 3097.14 (Ar C–H str.), 1608.79 (C=N str.), 1562.79 (CH=N str.), 1229.92 (C-N str.), 879.48 (C-H def. monosubstituted), 752.19 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 6.563-6.793 (m, 10H, Ar-H), 9.865 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 267.7 (18) $[M+1]^+$, 266.7 (35) $[M]^+$, 162.0 (26), 129.0 (100), 105.0 (22), 103.0 (24), 77.0 (9); Elemental analysis: Calcd. for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; Cl, 13.29; N, 10.50%; Found C, 72.03; H, 4.17; Cl, 13.28; N, 10.49%.

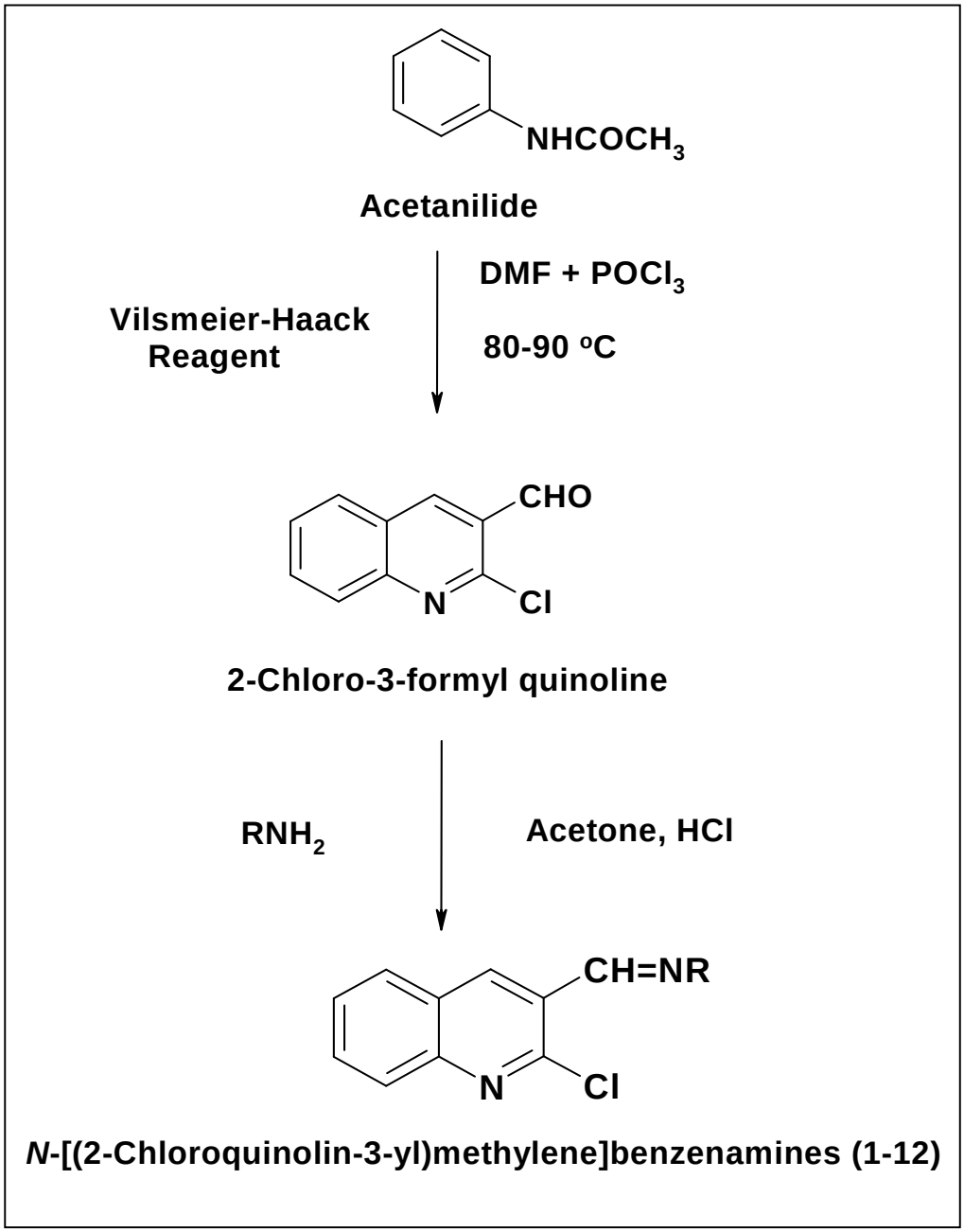
***N*-[(2-Chloroquinolin-3-yl)methylene]-2′-methoxybenzenamine, 2:** IR (KBr) ν: 3049.25 (Ar C–H str.), 2919.10 (C–H str.), 1602.43 (C=N str.), 1528.51 (CH=N str.), 1276.79 (C-N str.), 1151.42 (C-O-C, str.), 796.37 (C-H def. *o*-disubstituted), 748.33 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 3.936 (s, 3H, OCH_3), 6.541-6.780 (m, 10H, Ar-H), 9.870 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 297.7 (19) $[M+1]^+$, 296.7 (33) $[M]^+$, 189.0 (21), 162.0 (34), 129.0 (100), 104.0 (19), 103.0 (32), 77.0 (13); Elemental analysis**:** Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; Cl, 11.95; N, 9.44; O, 5.39%; Found C, 68.49; H, 4.47; Cl, 11.77; N, 9.41; O, 5.35%.

***N*-[(2-Chloroquinolin-3-yl)methylene]-4′-methoxybenzenamine, 3:** IR (KBr) ν: 3058.89 (Ar C–H str.), 2975.96 (C–H str.), 1596.59 (C=N str.), 1517.87 (CH=N str.), 1238.21 (C-N str.), 1150.25 (C-O-C str.), 825.30 (C-H def. *p*-disubstituted), 738.69 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 3.838 (s, 3H, OCH_3), 6.242-6.880 (m, 10H, Ar-H), 9.792 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 297.7 (17) $[M+1]^+$, 296.7 (29) $[M]^+$, 189.0 (23), 162.0 (37), 129.0 (100), 104.0 (18), 103.0 (33), 77.0 (12); Elemental analysis: Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; Cl, 11.95; N, 9.44; O, 5.39%; Found C, 68.58; H, 4.48; Cl, 11.94; N, 9.42; O, 5.37%.

***N*-[(2-Chloroquinolin-3-yl)methylene]benzylamine, 4:** IR (KBr) ν: 3056.89 (Ar C–H str.), 2965.96 (C–H str.), 1610.35 (C=N str.), 1579.59 (CH=N str.), 1231.01 (C-N str.), 844.76 (C-H def. monosubstituted), 748.66 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 2.571 (s, 2H, CH_2), 6.532-6.797 (m, 10H, Ar-H), 9.862 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 281.7 (12) $[M+1]^+$, 280.7 (41) $[M]^+$, 189.0 (25), 162.0 (31), 129.0 (100), 119.0 (11), 103.0 (23), 92.0 (13),

77.0 (11); Elemental analysis: Calcd. for $C_{17}H_{13}ClN_2$: C, 72.73; H, 4.67; Cl, 12.63; N, 9.98%; Found C, 72.71; H, 4.63; Cl, 13.62; N, 9.97%.

SCHEME I



4′-[(2-Chloroquinolin-3-yl)methyleneamino]benzoic acid, 5: IR (KBr) ν: 3328.10 (O–H str.), 3026.10 (Ar C–H str.), 1650.95 (C=O str.), 1602.74 (C=N ring str.), 1573.81 (CH=N str.), 1271.01 (C-N str.), 849.48 (C-H def. *p*-disubstituted) 751.47 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 6.532-6.797 (m, 10H, Ar-H), 9.762 ppm (s, 1H, CH=N), 10.471 (s, 1H, -COOH); ESI full mass-MS m/z (%): 311.0 (9) $[M+1]^+$, 310.0 (28) $[M]^+$, 189.0 (12), 162.0 (21), 129.0

(100), 121.0 (23), 77.0 (18); Elemental analysis: Calcd. for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; Cl, 11.41; N, 9.02; O, 10.30%; Found C, 65.70; H, 3.56; Cl, 11.39; N, 9.04; O, 10.31%.

***N*-[(2-Chloroquinolin-3-yl)methylene]-4′-fluorobenzenamine, 6:** IR (KBr) ν : 3097.47 (Ar C–H str.), 1610.45 (C=N str.), 1571.88 (CH=N str.), 1241.72 (C-N str.), 1164.92 (C-F str.), 828.91 (C-H def. *p*-disubstituted), 754.12 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 6.632-7.123 (m, 10H, Ar-H), 9.871 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 285.0 (23) $[M+1]^+$, 284.0 (36) $[M]^+$, 189.0 (18), 162.0 (24), 129.0 (100), 104.0 (14), 95.0 (28), 77.0 (8); Elemental analysis: Calcd. for $C_{16}H_{11}ClN_2$: C, 68.35; H, 4.05; Cl, 11.87; F, 6.36; N, 9.38%; Found. C, 68.32; H, 4.02; Cl, 11.81; F, 6.33; N, 9.35%.

***N*-[(2-chloroquinolin-3-yl)methylene] 4′-bromobenzenamine, 7:** IR (KBr) ν : 3026.10 (Ar C–H str.), 1602.74 (C=N str.), 1573.81 (CH=N str.), 1271.00 (C-N str.), 826.95 (C-H def. *p*-disubstituted), 751.47 (C-Cl str.), 578.60 cm^{-1} (C-Br str.); ^{1}HNMR (DMSO-d_6): δ 6.832-7.752 (m, 10H, Ar-H), 9.784 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 344.6 (18) $[M+1]^+$, 343.6 (21) $[M]^+$, 189.0 (12), 162.0 (19), 154.9 (16), 129.0 (100), 77.0 (14); Elemental analysis: Calcd. for $C_{17}H_{12}BrClN_2$: C, 56.77; H, 3.36; Br, 22.22; Cl, 9.86; N, 7.79%;Found C, 56.73; H, 3.35; Br, 22.20; Cl, 9.84; N, 7.78%.

2′,3′-Dichloro-*N*-[(2-chloroquinolin-3-yl)methylene]benzenamine, 8: IR (KBr) ν: 3024.18 (Ar C–H str.), 1596.95 (C=N str.), 1566.97 (CH=N str.), 1222.79 (C-N str.), 879.48 (C-H def. 1,2,3-trisubstituted), 752.19 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 6.701-7.084 (m, 10H, Ar-H), 9.802 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 334.9 (17) $[M+1]^+$, 333.9 (22) $[M]^+$, 189.0 (12), 162.0 (19), 144.9 (26), 129.0 (100), 111.0 (19), 77.0 (13); Elemental analysis Calcd. for $C_{17}H_{11}Cl_3N_2$: C, 58.40; H, 3.17; Cl, 30.42; N, 8.01%;Found C, 58.44; H, 3.15; Cl, 30.38; N, 8.05%.

3′,4′-Dichloro-*N*-[(2-chloroquinolin-3-yl)methylene]benzenamine, 9: IR (KBr) ν: 3070.46 (Ar C–H str.), 1610.45 (C=N str.), 1531.13 (CH=N str.), 1267.79 (C-N str.), 792.40 (C-H def. ,1,3,4-trisubstituted), 751.35 cm^{-1} (C-Cl str.);^{1}H NMR (DMSO-d_6): δ 6.832-7.197 (m, 10H, Ar-H), 9.752 ppm (s, 1H, CH=N);ESI full mass-MS m/z (%): 334.9 (15) $[M+1]^+$, 333.9 (38) $[M]^+$, 189.0 (9), 162.0 (25), 144.9 (36), 129.0 (100), 111.0(18), 77.0 (11);Elemental analysis: Calcd. for $C_{17}H_{11}Cl_3N_2$: C, 58.40; H, 3.17; Cl, 30.42; N, 8.01%;Found C, 58.41; H, 3.16; Cl, 30.43; N, 8.02%.

2′-[(2-Chloroquinolin-3-yl)methyleneamino]benzenethiol, 10: IR (KBr) ν: 3062.83 (Ar C–H str.), 1606.41 (C=N str.), 1571.59 (CH=N str.), 1235.21 (C-N str.), 1153.35 (C-S str), 771.19 (C-Cl str.), 738.6 cm^{-1} (C-H def. *o*-disubstituted);^{1}H NMR (DMSO-d_6): δ 2.848 (s, 1H, SH), 7.129-7.402 (m, 10H, Ar-H), 9.880 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 299.0 (13) $[M+1]^+$, 298.0 (31) $[M]^+$, 189.0 (28), 162.0 (16), 129.0 (100), 109.0 (21), 77.0 (12); Elemental analysis: Calcd. for $C_{17}H_{13}ClN_2S$: C, 65.27; H, 4.19; Cl, 11.33; N, 8.96; S, 10.25% ; Found C, 65.70; H, 3.56; Cl, 11.39; N, 9.04; O, 10.31%.

***N*-[(2-Chloroquinolin-3-yl)methylene]-4′-nitrobenzenamine, 11:** IR (KBr) ν: 3052.13 (Ar C–H str.), 1609.75 (C=N str.), 1579.59 (CH=N str.), 1399.30 (Ar-NO_2), 1279.51 (C-N str.), 804.56 (C-H def. *p*-disubstituted), 744.83 cm^{-1} (C-Cl str.); ^{1}H NMR (DMSO-d_6): δ 6.545-6.785 (m,

10H, Ar-H), 9.878 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 312.0 (19) $[M+1]^+$, 311.0 (42) $[M]^+$, 189.0 (26), 162.0 (15), 129.0 (100), 122.0 (21), 77.0 (12); Elemental analysis: Calcd. for $C_{16}H_{10}ClN_3O_2$: C, 61.65; H, 3.23; Cl, 11.37; N, 13.48; O, 10.27%; Found C, 61.63; H, 3.21; Cl, 11.35; N, 13.45; O, 10.23%.

***N*-[(2-Chloroquinolin-3-yl)methylene]-2′-nitrobenzenamine, 12:** IR (KBr) ν: 3072.16 (Ar C–H str.), 1605.14 (C=N str.), 1531.53 (CH=N str.), 1427.36 (Ar-NO_2), 1276.79 (C-N str.), 747.07 (C-Cl str.), 737.42 cm^{-1} (C-H def. *o*-disubstituted); ^1H NMR (DMSO-d_6): δ 6.646-7.083 (m, 10H, Ar-H), 9.879 ppm (s, 1H, CH=N); ESI full mass-MS m/z (%): 312.0 (11) $[M+1]^+$, 311.0 (41) $[M]^+$, 189.0 (22), 162.0 (13), 129.0 (100), 122.0 (18), 77.0 (8); Elemental analysis: Calcd. for $C_{16}H_{10}ClN_3O_2$: C, 61.65; H, 3.23; Cl, 11.37; N, 13.48; O, 10.27%; Found C, 61.66; H, 3.22; Cl, 11.34; N, 13.42; O, 10.26%.

Evaluation of antimalarial activity

The *in-vitro* antimalarial assay was carried out in 96 well microtiter plates according to the micro assay of Rieckmann [11]. The culture of *P. falciparum* NF-54 strain is routinely being maintained in medium RPMI-1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum [12]. The asynchronous parasite of *P. falciparum* was synchronized after 5% D-sorbitol treatment to obtain parasitized cells harboring only the ring stage [13]. For carrying out the assay, an initial ring stage parasitaemia of ≈1% at 3% hematocrit in total volume of 200 µL of medium RPMI-1640 was uniformly maintained. The test compound in 20 µL volume at the required concentration (ranging between 0.25 µg and 50 µg/mL) in duplicate wells, were incubated with parasitized cell preparation at 37 ºC in candle jar. After 36–40 hr incubation, the blood smears from each well were prepared and stained with giemsa stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of compounds. The tested concentration, which inhibits the complete maturation into schizonts, was recorded as the minimum inhibitory concentration (MIC). Chloroquine was used as the standard reference drug. Activity data of all the synthesized compounds is shown in **Table I**.

RESULTS AND DISCUSSION

Acetanilide was chosen as the parent molecule in our reaction strategy **(Scheme I)**. 2-Chloro-3-formyl quinoline was prepared from acetanilide. Thus acetanilide on treatment with Vilsmeier-Haack reagent gave 2-chloro-3-formyl quinoline in excellent yield. 2-Chloro-3-formyl quinoline with different substituted aryl amines were refluxed for 16-22 hr in acetone in presence of concentrated hydrochloric acid. The nucleophilic attack of the amino group on the formyl group leads to form the Schiff's bases of titled compounds (1-12) in good yield. It was observed that the reaction did not proceed without the addition of a few drops of concentrated hydrochloric acid. The % yields, reaction time and R_f values are shown in **Table I**.

The structures of the compounds were ascertained from the spectroscopic data and elemental analysis. The ^1H NMR spectrum showed the presence of the carbimino (-CH=N-) proton due to linkage with –N= and conjugated double bond system at δ = 9.75-9.89 ppm. The IR spectrum showed the absence of aldehydic C=O peak and the presence of CH=N- stretching vibration at

1560-1580 cm^{-1} confirmed the attachment of amino group of aryl amines to formyl group of quinoline nucleus.

Table I: Physical, analytical characterization and *in vitro* antimalarial screening data of the synthesized compounds (1-12)

Comp. No.	R	Reaction Time (hr)	Yield (%)	m.p. (°C)	R_f Value*	MIC** (µg/mL)
1	C_6H_5	16	68	283-285	0.72	30
2	2-OCH_3.C_6H_4	18	58	183-184	0.64	10
3	4-OCH_3 C_6H_4	17	61	193-194	0.69	20
4	C_6H_5.CH_2	18	44	225-226	0.59	>50
5	4-COOH.C_6H_4	16	55	187-188	0.71	15
6	4-F.C_6H_4	18	45	228-229	0.65	50
7	4-Br.C_6H_4	18	49	220-221	0.53	>50
8	2,3-Cl_2.C_6H_3	22	48	195-196	0.69	10
9	3,4-Cl_2.C_6H_3	21	42	192-193	0.66	2
10	2-SH.C_6H_4	20	52	184-185	0.62	35
11	2-NO_2.C_6H_4	21	47	171-172	0.68	50
12	4-NO_2.C_6H_4	20	57	174-175	0.71	50

* Solvent system: *n*-Hexane: ethyl acetate (7:3 v/v)
**MIC: Minimum inhibiting concentration for the development of ring stage parasite into the schizont stage during 40 hr incubation. MIC of chloroquine >50 µg/mL.

Out of the screened compounds, compound **9** has lower MIC value among all the tested compounds. Compound **9** was found to be most potent with 2 µg/mL MIC value. Compounds **2, 3, 5, 6, 8, 9, 10, 11** and **12** were also potent with 10 µg/mL, 20 µg/mL, 15 µg/mL,50 µg/mL, 10 µg/mL, 35 µg/mL, 50 µg/mL and 50 µg/mL respectively Compounds **4** and **7** were less potent with >50 µg/ml.

CONCLUSION

A series of 12 compounds were synthesized and screened against *P. falciparum* NF-54 strain. Out of the twelve screened compounds, compound **9** showed MIC of 2 µg/mL concentration and compounds **2, 3, 5** and **8** have shown MIC in the range between 10 and 20 µg/mL. The compounds **1, 6, 10, 11** and 1**2** have shown MIC in the range between 30 and 50 µg/mL. The compounds **4** and **7** have shown MIC of >50 µg/mL. Interestingly, the compound **9** shows better antimalarial activity indicated that introduction of chlorine atom into the 2- and 4-position of aryl ring of amine conferred a considerable antimalarial activity.

Acknowledgement
The authors are thankful to S.A.I.F., CDRI, Lucknow and IIT, Delhi for providing MASS and NMR spectroscopy facilities. S.K. Gupta acknowledges the financial support from AICTE.

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