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Synthesis and *In vitro* Antimalarial Activity of Some New 4-Aminoquinoline Mannich Base Derivatives

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ABSTRACT: A new series of 4-aminoquinoline Mannich base derivatives were prepared by selectively modifying the aliphatic diethyl amino function of isoquinewith different aliphatic/aromatic heterocyclic primary amino moieties at Mannich side chain. The synthesized compounds were characterized by their physical,analytical and spectral data, and screened for *in vitro* antimalarial activity against a chloroquine-sensitive 3D7 strain of *Plasmodium falciparum*. All the compounds showed *in vitro* antimalarial activity at the tested dose; which, however, was considerably less than that of the standard reference drug, chloroquine. Among the synthesized compounds, compounds with cyclohexyl (2f), methyl (2c) substitutions showed comparatively better activity than other compounds with n-octyl (2a), propyl (2b), 3-aminopropyl (2d) and furan-2-ylmethyl (2e) substitutions at aminomethyl side chain. The results clearly demonstrate that compound with saturated cycloalkylmoiety (cyclohexyl) exhibitedto some extentmore activity as compared to the compound with heterocyclicmoiety (furan-2-ylmethyl); and compounds with short chain alkyl substitutions (methyl, propyl etc.) were found to be more potent than that of compounds with long chain alkyl substitution (n-octyl).

KEYWORDS: 4-Aminoquinoline; Isoquine; Mannich base; Antimalarial; *Plasmodium falciparum*; alkyl chain.

Introduction

Malaria is a life-threatening infectious disease caused by protozoan parasites of the genus *Plasmodium*; *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*are four well known species of human malaria parasite[1, 2] and more recently another species, *P. knowlesi* has been documented[3]. It is one of the most widespread diseases worldwide particularly in tropical and subtropical regions; both from the point of view of mortality and morbidity[4,5]. Since past few decades, 4-aminoquinoline drugsespecially chloroquine (CQ) arein use for the treatment of malaria; but rapid development and spread of resistance of malaria parasite, especially *P. falciparum* towards CQ has limited their use in the treatment of malaria[6]. Amodiaquine(AQ), a 4-aminoquinoline Mannich base derivative has been introducedthereafter and was found effective against many CQ-resistant strains of *P. falciparum*; but clinical use of AQ has severely restricted because of having hepatotoxicity and agranulocytosis like severe side effects[7,8]. Further studies on amodiaquine structural analoques[9] have led to the development novel amodiaquineregioisomer, isoquine (IQ), which was found to be more effective than AQ and devoid of any severe side effects. However, structure activity relationship studies on 4-aminoquinoline antimalarial compounds suggested that 7-chloro-4-aminoquinoline nucleus is obligatory for antimalarial activity[10] and recent literature on amodiaquine structural analogues has reported that the presence of 4´ hydroxyl group within the aromatic ring imparts greater inherent antimalarial activity against chloroquine-resistant parasite. Moreover, interchange of the hydroxyl group and the Mannich side chain as in isoquine prevents oxidation to toxic metabolites while retaining desirable activity profile[9]. Based on this fact, we presumed to designing 4-aminoquinoline Mannich bases by selectively modifying the side chain amino group with primary aminesthat could improve the antimalarial activity and might be effective against resistant parasites. In the current work, some new derivatives of 4-aminoquinoline Mannich bases were synthesized and screened for *in vitro* antimalarial activity.

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Experimental

All the chemicals were of synthetic grade and commercially procured from Sigma-Aldrich Corporation (USA), Merck (Germany) or Spectrochem Pvt. Ltd. (India). 4,7-dichloroquinoline was obtained as gift sample from M/s. Mangalam Drug & Organics, Mumbai, India. Melting points of the synthesized compounds were determined in open capillaries on a Veego-MPI melting point apparatus

and are uncorrected. The purity of the compounds was checked on silica gel-G TLC plates. The spots were detected with iodine vapors on UV-light (254 nm). The UV-visible spectra (λ_{max} in nm) of synthesized compounds were obtained on a Hitachi U-2001UV-visible spectrophotometer. Infrared (IR) spectra were recorded using KBr on a Perkin-Elmer Spectrum RX-I FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSOon a Bruker AC-F 300 FT-NMR spectrometer using TMS as internal standard (Chemical shifts in δ, ppm). Mass spectra were obtained with a LC-MS Water 4000 ZQ instrument using atmospheric pressure ionization (API). Elemental microanalyses (CHN) were performed on a Perkin Elmer 2400 Series II CHNS/Oanalyzer.

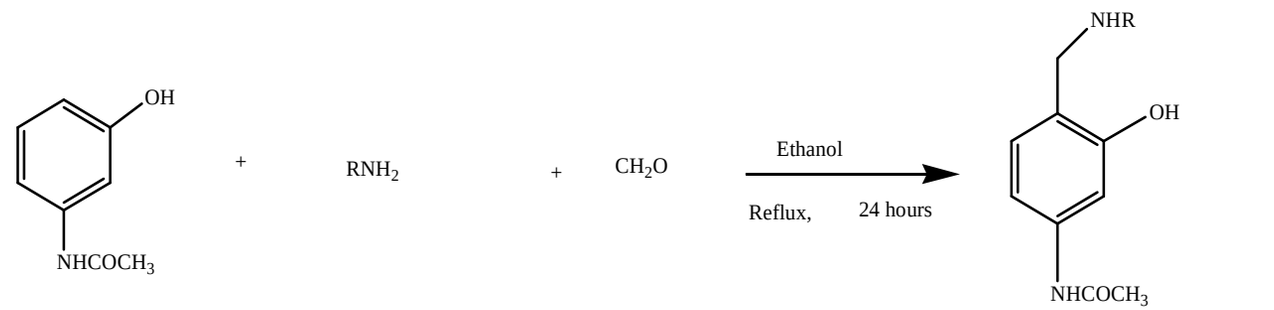
General method of Synthesis

The synthesis involves the preparation of Mannich basesfrom commercially available 3-hydroxyacetanilide (Scheme I) followed by hydrolysis of the amide function and subsequent coupling with 4,7-dichloroquinoline (Scheme II) yield the desired substituted Mannich bases of 4-aminoquinoline phenols [9].

Procedure

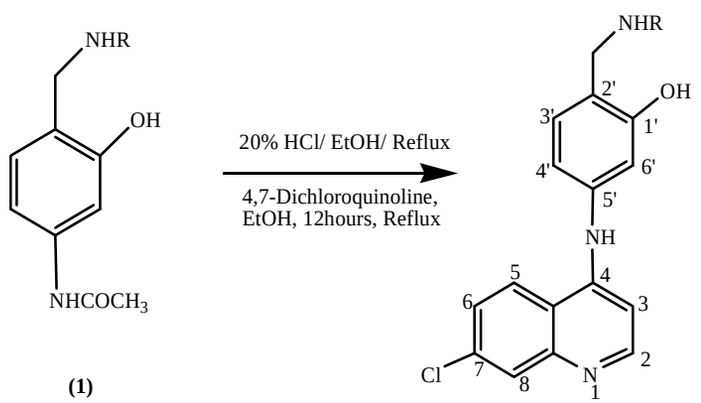
Step 1

A mixture of 3-Hydroxyacetanilide (6 gm, 39.69 mmol), appropriate primary amine (39.69 mmol) and aqueous formaldehyde (2.46 ml) in ethanol (28.29 ml) was heated under reflux for 24 hours and the solvent was removed under reduced pressure to obtain chocolate brown sticky solid. The crude semisolid product was purified by silica-gel Flash Column Chromatography (FCC) using 20-80% methanol/dichloromethane as eluent. The desired product was obtained aspale brown solid.



3-Acetamidophenol | Primary amine | Formaldehyde | *N*-(3-hydroxy-4-((substitutedamino) methyl)phenyl)acetamide **(1)**

Scheme 1



(1)

Comp. code	R
2a	n-octyl
2b	propyl
2c	methyl
2d	3-aminopropyl
2e	furan-2-ylmethyl
2f	Cyclohexyl

5-(7-chloroquinolin-4-ylamino) -2-((substitutedamino)methyl)phenol **(2a-f)**

Scheme 2

Step 2

A solution of N-(3-hydroxy-4-((substitutedamino) methyl) phenyl)acetamide, 1 (4.892 g, 16.67 mmol) in hydrochloric acid (20%, 27.3 ml) was heated under reflux for 6 hours. The solvent was then removed under reduced pressure and the resulting residue was coevaporated with ethanol. The residue was dissolved in ethanol (20 ml), 4,7-dichloroquinoline (0.005 mmol) was added, and then the mixture was under refluxed for 12 hour. The crude pale yellow solid was subsequently purified by silica-gel Flash Column Chromatography (FCC) using 20-80% Methanol/ dichloromethane as eluent to yield quinoline hydrochloride salt as a yellow solid. To liberate the free base compound, this solid was dissolved in distilled water (19.6 ml) and the solution was basified by careful addition of saturated sodium bicarbonate. Dichloromethane was added (109 ml), and the free base was extracted into the organic layer. Subsequent removal of solvent under reduced pressure yield desired solid final product (2a-f).

Spectral data

5-(7-chloroquinolin-4-ylamino)-2-((octylamino)methyl)phenol(2a):

UV spectrum (Methanol), λ_{max} (nm): 355. IR (KBr), υ (cm^{-1}): 3466 (O-H str., free –OH, Ar-OH); 3315(N-H str., >NH); 3015(Ar. C-H str.); 2927, 2858(C-H str., υ_{as}&υ_{s}>CH_2);1610, 1581, 1506, 1456(C=C str., Ar. ring); 1373, 1309(Ar. C-N str.); 1074 (Ar. C-Clstr.). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.70 (d, 1H, J=5.50Hz, quinoline-H_2); 7.03 (d, 1H, J=5.50Hz, quinoline-H_8); 8.01 (d, 1H, J=2.20Hz, quinoline-H_5); 7.84(d, 1H, J=8.90Hz, quinoline-H_6);7.50 (s, 1H, NH);7.43 (dd, 1H, J=9.16, 2.04Hz, quinoline-H_3); 6.95 (d, 2H, J=7.92Hz, CH_2); 6.76 (d, 2H, J=2.05 Hz, CH_2); 6.54 (bs, 1H, OH); 1.29(m, 8H, CH_2 $CH_2CH_2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):161.67, 154.92, 152.50, 149.61, 142.87, 127.71, 119.89, 107.60, 49.40, 29.21. MS (API), m/z (%):411.2 (100), $[M]^+$.

5-(7-chloroquinolin-4-ylamino)-2-((propylamino)methyl)phenol(2b):

UV spectrum (Methanol), λ_{max} (nm): 340. IR spectrum (KBr), υ (cm^{-1}): 3462 (O-H str., free –OH, Ar-OH); 3340(N-H str., >NH); 3015(Ar. C-H str.);2968, 2845 (C-H str., υ_{as}&υ_{s}>CH_2);1604, 1575, 1523, 1448, 1082(C=C str., Ar. ring); 1374 (Ar. C-N str.); 1077 (Ar. C-Clstr.).^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.71 (d, 1H, J=5.40Hz, quinoline-H_2), 8.02 (d, 1H, J=2.42Hz, quinoline-H_8),7.84(d, 1H, J=8.8Hz, quinoline-H_5), 7.84 (d, 1H, J=8.90Hz, quinoline-H_6), 7.50 (s, 1H, NH); 7.45 (dd, 1H, J=8.80, 2.32Hz, quinoline-H_3), 6.98 (d, 1H, J=7.96 Hz, CH_2), 6.75(d, 1H, J=2.21Hz, CH_2), 6.51 (bs, 1H, OH), 1.55(m, 4H, NCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):159.78, 148.51,134.82, 127.41, 124.60, 119.40, 110.39, 57.82, 39.95. MS (API), m/z (%):341.8 (100), $[M]^+$.

5-(7-chloroquinolin-4-ylamino)-2-((methylamino)methyl)phenol (2c)

UV spectrum (Methanol), λ_{max} (nm): 331. IR spectrum (KBr), υ (cm^{-1}): 3466 (O-H str.,free –OH, Ar-OH); 3310(N-H str., >NH); 3016 (Ar. C-H str.);2978, 2883(C-H str., υ_{as}&υ_{s}>CH_2);1608, 1575, 1517, 1446 (C=C str., Ar. ring); 1345(Ar. C-N str.); 1080(Ar. C-Clstr.). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.70 (d, 1H, J=5.50Hz, , quinoline-H_2), 8.17 (d, 1H, J=8.6Hz, quinoline-H_8),8.02(d, 1H, J=2.42Hz, quinoline-H_5), 7.86(d, 1H, J=8.4Hz, quinoline-H_6), 7.51 (s, 1H, NH); 7.45(dd, 1H, J=8.80, 2.3Hz, quinoline-H_3), 6.98 (d, 1H, J=7.96Hz, CH_2), 6.75 (d, 1H, J=2.21 Hz,CH_2), 6.63 (d, 1H, J=7.94 Hz, CH_2), 6.58 (bs, 1H, OH),2.49(s,3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):159.78, 149.00, 134.36, 129.74, 127.48, 123.72, 119.20, 113.03, 109.46, 101.61, 62.68, 45.80. MS (API), m/z (%): 313.8 (100), $[M]^+$.

5-(7-chloroquinolin-4-ylamino)-2-((3-aminopropylamino)methyl) phenol (2d)

UV spectrum (Methanol), λ_{max} (nm): 339. IR spectrum (KBr), υ (cm^{-1}): 3446 (O-H str., free –OH, Ar-OH); 3325(N-H str., >NH);3061(Ar. C-H str.); 2953, 2893(C-H str., υ_{as}&υ_{s}>CH_2);1605, 1546, 1502, 1445(C=C str., Ar. ring);1309(Ar. C-N str.); 1063(Ar. C-Cl str.);^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.67 (d, 1H, J=4.8Hz, , quinoline-H_2), 8.00 (d, 1H, J=2.19Hz, quinoline-H_8),7.84 (d, 1H, J=8.8Hz, quinoline-H_5), 7.87(dd, 1H, J=8.80, 2.20 Hz, quinoline-H_6), 7.51 (s, 1H, NH); 7.44(d, 1H, J=5.14Hz, quinoline-H_3) 6.98 (d, 1H, J=7.96Hz,CH_2), 6.74(d, 1H, J=2.21Hz, CH_2), 6.65 (d, 1H, J=8.00Hz, CH_2), 6.56 (bs, 1H, OH), 3.81(s,2H, CH_2), 1.67(m, 6H, $NCH_2CH_2CH_2N$):^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):158.88, 149.99, 140.71, 134.94, 129.75, 127.16, 121.21, 119.24, 113.13, 109.18, 101.58 ,64.36, 39.95. MS (API), m/z (%): 313.8 (100), $[M]^+$.

5-(7-chloroquinolin-4-ylamino)-2-(((furan-2-ylmethylamino)methyl)phenol(2e)

UV spectrum (Methanol), λ_{max} (nm): 265. IR spectrum (KBr), υ (cm^{-1}): 3456 (O-H str., free –OH, Ar-OH); 3325(N-H str., >NH);3061 (Ar. C-H str.);2953, 2893(C-H str., υ_{as}&υ_{s}>CH_2);1622, 1546, 1502, 1475 (C=C str., Ar. ring); 1309 (Ar. C-N str.); 1063 (Ar. C-Cl str.). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.71 (d, 1H, J=4.8Hz, , quinoline-H_2), 7.96 (d, 1H, J=4.12 Hz, quinoline-H_8),7.84 (d, 1H, J=8.8Hz, quinoline-H_5), 7.72 (dd, 1H, J=8.7, 2.23

Hz, quinoline-H_6), 7.49 (s, 1H, NH); 7.46 (d, 1H, J=5.14Hz, quinoline-H_3); 7.30 (d, 1H, J= 4.8 Hz, furan-H_3), 6.97 (d, 1H, J=7.56Hz, CH_2), 6.74(d, 1H, J=2.22 Hz, CH_2), 6.65 (d, 1H, J=6.8Hz, CH_2), 6.56 (bs, 1H, OH), 6.30 (d, 1H, J=16.00 Hz, furan-H_4), 6.24 (d, 1H, J= 15.20 Hz, furan-H_5), 3.75(s,2H, CH_2), 3.62 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):156.27, 149.46, 143.05, 134.31, 129.40, 127.46, 123.25, 119.31, 110.89, 108.94, 107.06, 101.82, 48.58. MS (API), m/z (%):379.3 (100), $[M]^+$.

5-(7-chloroquinolin-4-ylamino)-2-((cyclohexylamino)methyl)phenol (2f):

UV spectrum (Methanol), λ_{max} (nm): 313. IR spectrum (KBr), υ (cm^{-1}): 3462 (O-H str., free –OH, Ar-OH); 3349 (N-H str., >NH); 3037 (Ar. C-H str.); 2927, 2836 (C-H str., υ_{as}&υ_s>CH_2); 1609, 1573, 1451 (C=C str., Ar. ring); 1372 (Ar. C-N str.); 1082 (Ar. C-Cl str.). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.68 (d, 1H, J=5.92Hz, quinoline-H_2), 7.96 (d, 1H, J=4.12 Hz, quinoline-H_8),7.71 (d, 1H, J=7.68Hz, quinoline-H_5), 7.53(dd, 1H, J=8.8, 2.23 Hz, quinoline-H_6), 7.49 (s, 1H, NH); 7.19(d, 1H, J=5.14Hz, quinoline-H_3); 6.97 (d, 1H, J=7.56Hz, CH_2), 6.75(d, 1H, J=2.22Hz, CH_2), 6.64 (d, 1H, J=6.8Hz, CH_2), 6.50 (bs, 1H, OH); 3.76(s,2H, CH_2); 1.8 (m,10H, cyclohexyl). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):157.21, 149.39, 143.05, 140.42, 134.76, 129.40, 127.16, 119.31, 113.58, 101.82, 55.41, 49.26, 38.94, 28.37. MS (API), m/z (%):381.8 (100), $[M]^+$.

***In vitro* antimalarial screening**

The synthesized compounds, 2a-fwere screened for *in vitro* antimalarial activity against a CQ-sensitive strain of *Plasmodium falciparum* (3D7) in the Regional Medical Research Centre (I C M R), N E Region, Dibrugarh, Assam, India.

All the synthesized compounds were evaluated for *in vitro* antimalarial activity. Continuous culture of CQ-sensitive strain of *P. falciparum* (3D7) was maintained *in vitro* in O+ human red blood cells diluted to 6% haematocrit in RPMI 1640 medium supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate, gentamycin (40 μg/ml), amphotericin-B (0.25 μg/ml), and 10% human AB+ serum [11]. Incubations were done at 37^{o}C and 5% CO2 level in a modular incubator. D-sorbitol synchronized[12] 1% ring stage parasitaemia in 3% haematocrit was used for antimalarial assays using 96 well microtitreplate. A stock solution of 5 mg/ml of the test compound was prepared in DMSO and subsequent dilutions were made with incomplete RPMI in duplicate. All test compounds were assayed at a fixed dose of 50 μg/ml. Each test well of the microtitre plate contained 20 μl of the compound and 180 μl of 1% ring stage parasitaemia in 3% haematocrit. In addition, drug free negative control to assess the parasite growth and chloroquinediphosphate, at predetermined 50% inhibitory concentration (IC_{50}) dose, as positive control to assess the integrity of the assay were also maintained in duplicate in the microtitre plate. After 40 h of incubation the smears were prepared from each well, stained with 3% Giemsa and scanned under light microscope to ascertain percentage dead rings and trophozoites by examining a minimum of 400 asexual parasites.

Results and discussion

In the present study, a new series of 4-aminoquinolone Mannich base derivatives were synthesizedby replacement of 4′-diethylamino function of Isoquine by a 4′-primary amino function; and evaluated for antimalarial activity. The Purity of the synthesized compounds was ascertained by melting point determinations and Silica gel G TLC. The structural assignment these compounds were made on the basis of UV, FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectral studies and elemental analyses report. The physical and analytical data of the synthesized compounds (2a-f) are depicted in Table 1.

The spectral data as depicted in experimental section are in close agreement with the structures of the synthesized compounds. All the compounds in methanol exhibited characteristic absorption maxima (λ_{max} in nm) in the range between 265-355 nm. The shift of λ_{max} towards longer wavelength indicates the presence of strong chromophoricquinoline moiety, auxochrome (-NH_2) substituted hydrocarbon chain etc. in the parent structure of the compounds. The infrared spectral data showed characteristic absorption bands for phenolic –OH (free), 2^o amino function (>NH), aryl -C=C-, >CH_2 of side chain, aryl C–N and aromatic C–Clmoieties etc. which confirms the anticipated structure of the synthesized compounds, 2a-f. The assignment of protons is fully supported by the characteristic chemical shift values for different protons of (=CH-) quinoline ring system and phenolic ring; protons of >NH, -NH_2, aryl -OH and side chain methylenic (=CH_2) protons of synthesized compounds. The ^{13}C resonance data of different carbon atoms of quinoline structure, =CH_2 and –NCH_3 and furan-2ylmethyl groups of side chain ascertain the corresponding structures of the synthesized compounds. The prominent molecular ion peaks, M^+ for all the compounds are in accordance with the anticipated mass of 2a-f.The results of CHN analyses were within the acceptable limits of the calculated values as depicted in experimental section.

Table 1 Physical and analytical data.

Comp.	Mol. Formula	Mol. Wt.	Yield (%)	M.P. (°C)	R_f value*	Elemental analysis (%) Found (Calculated)		
						C	H	N
2a	$C_{24}H_{30}N_3OCl$	411.2	72.62	141-143	0.89	68.92 (69.97)	7.82 (7.34)	9.13 (10.20)
2b	$C_{19}H_{20}N_3OCl$	341.8	69.82	270-273	0.44	65.56 (66.76)	5.84 (5.90)	11.98 (12.29)
2c	$C_{18}H_{20}N_3OCl$	313.8	67.21	237-238	0.83	66.01 (66.07)	5.92 (5.14)	13.34 (13.39)
2d	$C_{19}H_{21}N_4OCl$	356.3	74.02	135-136	0.62	62.01 (63.95)	5.33 (5.93)	16. 27 (15.70)
2e	$C_{21}H_{18}N_3O_2Cl$	379.3	71.45	239-242	0.69	65.41 (66.40)	5.67 (4.78)	9.98 (11.06)
2f	$C_{23}H_{25}N_2OCl$	381.8	68.67	178-179	0.53	72.54 (72.59)	6.68 (6.62)	6.95 (7.35)

* Acetone: MeOH= 2:3

The results of *in vitro* antimalarial screening depicted in Table 2 clearly revealed that all the synthesized compounds showed activity against chloroquine-sensitive *Plasmodium falciparum*3D7 strain at the tested dose which, however, was considerably less than that of the standard reference drug, chloroquine. Among the synthesized compounds, compounds with cyclohexyl (2f), methyl (2c) substitutions showed comparatively better activity than other compounds with n-octyl (2a), propyl (2b), 3-aminopropyl (2d) and furan-2-ylmethyl (2e) substitutions at aminomethyl side chain. The results clearly demonstrate that compound with saturated cycloalkyl moiety (cyclohexyl) exhibited to some extent more activity as compared to the compound with heterocyclic ring moiety (furan-2-ylmethyl); and compounds with short chain alkyl substitutions (methyl, propyl etc.) were found to be more potent than that of compounds with long chain alkyl substitution (n-octyl).

Table 2 *In vitro* antimalarial activity data.#

Sl. No.	Comp. code	Dosage (µg/ml)	% Dead rings + Trophozoites*
1	2a	50	35.3
2	2b	50	31.6
3	2c	50	39.0
4	2d	50	33.3
5	2e	50	27.0
6	2f	50	43.3
7	Chloroquine@	0.4	57.6

#Test strain: Chloroquine-sensitive *Plasmodium falciparum* (3D7)

*mean of three replicates and counted against 400 asexual parasites per replicate

@Reference standard

It has been reported in literature[9] that replacement of the diethyl functional moiety at the Mannich side chain 4-aminoquinoline phenols with the metabolically stable aliphatic side chain as well as heterocyclic ring as in morpholinyl modifications led to a substantial increase in the antimalarial activity. Although the activity of the synthesized compounds was found to be quite low as compared to the standard drug, our present investigation provide the basis of designing new 4-aminoqunoline Mannich base derivatives with suitable structural modification in the side chain. This strategy may lead to the development of novel lead molecules in the discovery of novel isoquineanalogues which would represent safe, cheap and effective antimalarials with improved activity profile, enhanced metabolic stability and less toxicity.

Conclusion

The present work investigates the synthesis and antimalarial activity evaluation of some new derivatives of 4-aminoquinoline Mannich bases. These compounds are newly synthesized and have not been reported earlier. The synthesized compounds were found to be much less potent than the standard reference drug, chloroquine at the tested dose.

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