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Synthesis and antimalarial activity of Baylis-Hillman adducts from substituted 2-chloroquinoline-3-carboxaldehydes

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Abstract

Various quinoline carboxaldehydes were prepared from corresponding anilides using classical Vilsmeier-Haack reaction conditions and transformed into their Baylis-Hillman adducts. The synthesized Baylis-Hillman adducts were screened for their *in vitro* antimalarial activity against *Plasmodium falciparum*. Most of the compounds out of 21 compounds synthesized and screened exhibited substantial antimalarial activity.

Keywords: 2-chloroquinoline-3-carboxaldehyde; antimalarial activity; Baylis-Hillman adducts; crystal structure; Vilsmeier-Haack reaction.

Introduction

Derivatives of pyridine and its fused analogs are an important class of heterocyclic compounds as a result of their biological activities (Roth and Kleemann, 1988; MDDR, 2004). Quinolines are also known to possess a wide range of biological properties, including antimicrobial, anti-inflammatory, analgesic, antimalarial, anticancer, antiviral, antileishmanial and antitubercular activities (Gantier et al., 1996; Michael, 1997, 2005, 2007; Bilker et al., 1998; Chauhan and Srivastava, 2001; Suryawanshi et al., 2008; Bandgar et al., 2010; Hans et al., 2010; Tomar et al., 2010; Venkatesan and Sumathi, 2010). It is particularly noteworthy that novel quinoline derivatives have recently been reported as possible antimalarial agents (Vlahov et al., 1990; Iwaniuk et al., 2009; Hayat et al., 2011; Kumar et al., 2011b). Continuing our interest in the Baylis-Hillman (BH) reaction (Narender et al., 2006a, 2009; Ravinder et al., 2009, 2010) and in heterocycles synthesis (Narender et al., 2006b; Srinivas et al., 2009; Kumar et al., 2011a) and with the purpose of exploring biological activity, we synthesized a series of BH adducts, originating from chloroquinoline carboxaldehydes. As part of our study, the BH adducts were screened for their *in vitro* antimalarial activity against *Plasmodium falciparum*.

Results and discussion

The synthesis of various BH adducts are outlined in Scheme 1. These adducts were selected because of their structural similarity with chloroquine, a known drug used for the control of malaria (Natarajan et al., 2008). The first step in the study was the acetylation of readily available anilines leading to their corresponding anilides. The anilides were subjected to a Vilsmeier-Haack reaction using dimethylformamide (DMF) and phosphorus oxychloride (Scheme 1) to yield the chloroquinoline carbaldehydes (**1a–1k**) with very good yields (Meth-Cohn et al., 1981; Lavergne et al., 1998; Gangadas et al., 2006). The chloroquinoline carbaldehydes were subjected to the BH reaction (Table 1) to produce BH adducts (**2–22**) in excellent yields. Various bases and solvents were employed in conducting the BH reaction (Table 2). The best condition was developed by mixing the starting materials with DABCO at room temperature in solvent free conditions. All BH adducts were characterized by spectroscopic techniques [^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, infrared (IR) and mass spectrometry]. Compounds **20** (Figure 1) and **4** (Figure 2) were additionally confirmed by single X-ray crystallographic analyses (Bruker, 2001; Sheldrick, 2008).

Thus, 21 BH compounds **2–22** were screened for *in vitro* antimalarial activity (Trager and Jensen, 1976; Biswas, 2001) against a chloroquine sensitive (FDL-J) strain of *P. falciparum* at different doses starting from 50 μg/well to 0.0032 μg/well with five-fold serial dilutions. The doses were kept constant for all compounds so that their activity profiles were comparable with each other. The results, IC_{50} and IC_{90}, are summarized in Table 3. An overwhelming number of the BH compounds were found to possess excellent anti-*Plasmodium* activity. Adducts **2–12** that contained a nitrile group were more active than adducts **13–22**, which included an ester group (Table 3). This is consistent with our earlier observation (Narender et al., 2005). BH adducts **3, 14, 15, 18** and **19**, which have an alkyl substituent, were less active compared with other compounds suggesting that the lower activity may have been caused by the combined effects of the alkyl substituent and ester end group.

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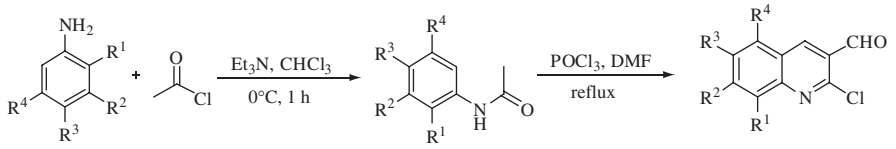
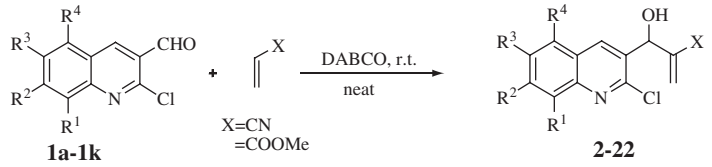


1a-1k



1a-1k **2-22**

	R^1	R^2	R^3	R^4
1a=H;	H;	H;	H;	
1b=H;	Me;	H;	H;	
1c=H;	H;	OMe;	H;	
1d=H;	OMe;	OMe;	H;	
1e=OMe;	H;	H;	OMe;	
1f=H;	H;	Me;	H;	
1g=H;	H;	i-Pr;	H;	
1h=Me;	H;	H;	H;	
1i=H;	Cl;	H;	H;	
1j=H;	F;	H;	H;	
1k=H;	Cl;	F;	H;	

	R^1	R^2	R^3	R^4
2=X=CN;	H;	H;	H;	
3=X=CN;	H;	Me;	H;	
4=X=CN;	H;	Me;	H;	
5=X=CN;	H;	OMe;	OMe	
6=X=CN;	OMe;	H;	H;	
7=X=CN;	H;	H;	Me;	
8=X=CN;	H;	H;	i-Pr;	
9=X=CN;	Me;	H;	H;	
10=X=CN;	H;	Cl;	H;	
11=X=CN;	H;	F;	H;	
12=X=CN;	H;	Cl;	F;	

	R^1	R^2	R^3	R^4
13=X=COOMe;	H;	H;	H;	
14=X=COOMe;	H;	Me;	H;	
15=X=COOMe;	H;	Me;	H;	
16=X=COOMe;	H;	OMe;	OMe;	
17=X=COOMe;	OMe;	H;	H;	
18=X=COOMe;	H;	H;	Me;	
19=X=COOMe;	H;	i-Pr;	H;	
20=X=COOMe;	Me;	H;	H;	
21=X=COOMe;	H;	Cl;	H;	
22=X=COOMe;	H;	F;	H;	

Scheme 1 Synthesis of Baylis-Hillman adducts form 2-chloroquinoline-3-carboxaldehydes.

Conclusions

In conclusion, 2-chloroquinoline based BH adducts have been synthesized and characterized. All the compounds were screened for *in vitro* antimalarial activity and found to exhibit substantial antimalarial activity. These molecules will be probed further for their anti-malarial properties.

Experimental section

All solvents were distilled and dried by standard procedures. Melting points were determined by using capillary melting point apparatus (VMP-AM) and were uncorrected. IR spectra were recorded by using a Thermo Nicolet Nexus 670 FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 MHz, Varian Inova 400 MHz or Inova 500 MHz FT spectrometer, using tetramethylsilane as an internal standard (chemical shift values in δ, coupling constants J in Hz). HRMS (ESI) data were recorded on a QSTAR XL high-resolution mass spectrometer. Gas chromatography-mass spectrometry (GC-MS) data were recorded on an Agilent 6890 series GC-MS system (column: Varian CP-Sil 8 CB, 5% phenyl, 95% PDMS, 30.0 m×250 µm×0.30 µm nominal). Column chromatography was performed by using silica gel (60–120 mesh).

General procedure for synthesis of Baylis-Hillman (BH) adducts

A mixture of methyl acrylate/acrylonitrile (10.4 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (3.4 mmol) were combined and stirred at room temperature for 5 min. To this mixture, 2-chloroquinoline-3-carboxaldehyde (5.2 mmol) was added and the mixture was stirred at room temperature for an appropriate length of time (Table 1). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, ethyl acetate (20 ml) was added to the reaction mixture and it was washed with water (4×10 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by passing through a small pad of silica gel (eluent:hexane:ethyl acetate). The same experimental procedure was adopted for the synthesis of other BH adducts.

2-[(2-Chloroquinolin-3-yl)(hydroxy)methyl]acrylonitrile (2) Yield: 97%; sandy brown solid; m.p. 113–115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 1H), 6.11 (s, 1H), 6.12 (s, 1H), 7.58 (t, J=8.3 Hz, 1H), 7.75 (t, J=8.3 Hz, 1H), 7.88 (d, J=8.3 Hz, 1H), 8.00 (d, J=8.3 Hz, 1H), 8.45 (s, 1H), ^{13}C NMR (75 MHz, DMSO-d_6) δ 70.0, 117.4, 124.6, 127.3, 128.0, 128.1, 128.9, 131.6, 132.7, 133.9, 137.8, 147.0, 148.4; IR (KBr) 3169, 2924, 2854, 2227, 1727, 1615, 1572, 1491, 1394, 1138, 1074, 1036, 821 cm^{-1}; MS (ESI): m/z=245 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{13}H_{10}ClN_2O$: 245.0481, found: 245.0474.

2-[(2-Chloro-7-methylquinolin-3-yl)(hydroxy)methyl]acrylonitrile (3) Yield: 95%; wheatish solid; m.p. 136–138°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H), 3.27 (s, 1H), 5.80 (s, 1H), 6.10 (s, 1H), 6.11 (s, 1H), 7.40 (d, J=8.3 Hz, 1H), 7.76 (d, J=8.3 Hz, 1H), 7.77 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.3, 69.5, 116.9, 124.2, 124.9, 126.3, 127.9, 129.6, 131.1, 133.1, 136.9, 141.3, 146.8, 147.8; IR (KBr): 3246, 3056, 2919, 2219, 1626, 1599, 1493, 1396, 1381, 1254, 1140, 1072, 1036, 806 cm^{-1}; MS (ESI): m/z=259 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{14}H_{12}ClN_2O$: 259.0638, found: 259.0627.

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Table 1 Baylis-Hillman adducts synthesized.

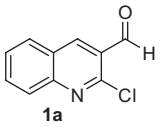
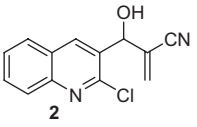
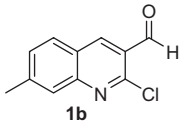
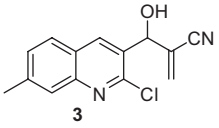
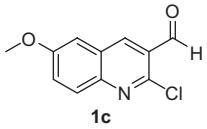
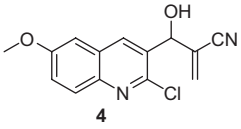
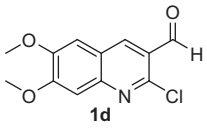
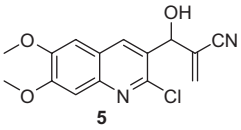
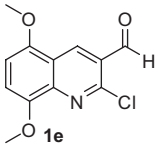
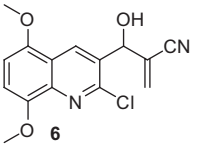
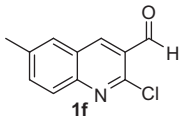
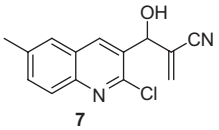
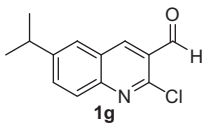
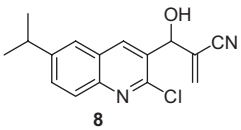
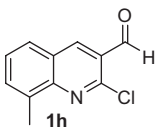
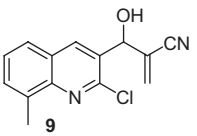
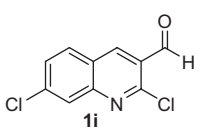
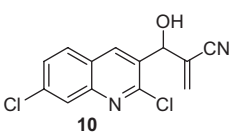
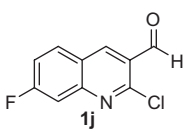
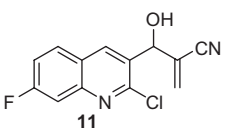
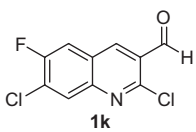
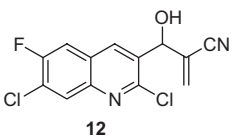
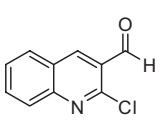
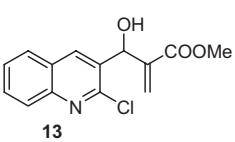
Entry	Aldehyde	Activated Olef in	BH adducts[a]	Time (h)	Yield (%)[b]
1	 **1a**		 **2**	2	97
2	 **1b**		 **3**	2.5	95
3	 **1c**		 **4**	1.5	94
4	 **1d**		 **5**	3	98
5	 **1e**		 **6**	1	95
6	 **1f**		 **7**	1	97
7	 **1g**		 **8**	1	97
8	 **1h**		 **9**	0.5	98
9	 **1i**		 **10**	2	97
10	 **1j**		 **11**	11	93
11	 **1k**		 **12**	1	93
12	 **1a**		 **13**	4	97

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Table 1 (Continued)

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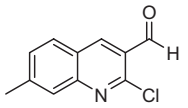
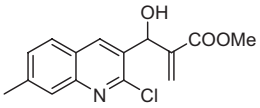
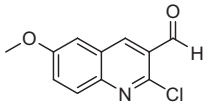
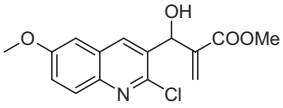
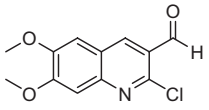
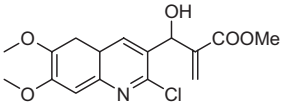
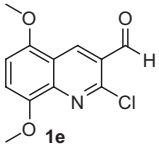
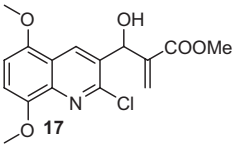
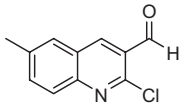
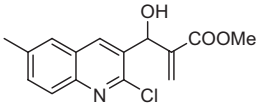
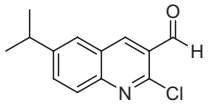
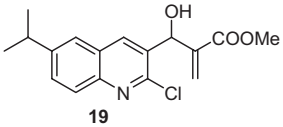
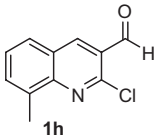
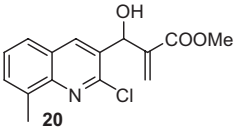
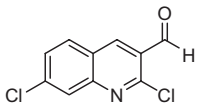
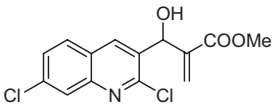
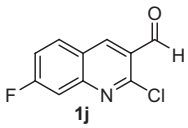
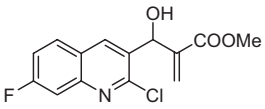
13	 **1b**		 **14**	5	91
14	 **1c**		 **15**	16	80
15	 **1d**		 **16**	120	89
16	 **1e**		 **17**	48	91
17	 **1f**		 **18**	4.5	95
18	 **1g**		 **19**	8	90
19	 **1h**		 **20**	6	96
20	 **1i**		 **21**	30	92
21	 **1j**		 **22**	36	90

[a]Each reaction was carried out by taking aldehyde (5.2 mmol), activated olefin (10.4 mmol) and DABCO (3.4 mmol) under neat condition; [b]isolated yields of the products.

2-[(2-Chloro-6-methoxyquinolin-3-yl)(hydroxy)methyl]acrylonitrile (4) Yield: 94%; wheatish solid; m.p. 127–129°C; ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6) δ 3.91 (s, 1H), 5.61 (d, J=4.8 Hz, 1H), 6.04 (s, 1H), 6.08 (s, 1H), 6.43 (d, J=4.8 Hz, 1H), 7.23 (d, J=2.9 Hz, 1H), 7.33 (dd, J=2.9, 9.7 Hz, 1H), 7.80 (d, J=9.7 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.6, 69.5, 106.1, 116.9, 123.4, 124.2, 128.1, 128.8, 132.2, 133.1, 136.0, 142.4, 145.1, 157.9; IR (KBr): 3546, 3163, 2958, 2915, 2227, 1622, 1589, 1498, 1383, 1340, 1272, 1172, 1092, 1043, 836 cm^{-1}; MS (ESI): m/z=275 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{14}H_{12}ClN_2O_2$: 275.0587, found: 275.0577.

Crystal data for compound **4**: triclinic, space group *Pi*, a=7.8029 (11) Å, b=9.2884 (13) Å, c=10.5342 (15) Å, α=92.582 (2)°, β=96.257 (2)°, γ=108.614 (2)°, *V*=716.65 (18) Å^3, *Z*=2, D_c=1.356 Mg m^{-3}, μ(Mo Kα)=0.275 mm^{-1}, F000=304, *T*=294(2) K. The total number of measured reflections was 6897. *GOF*=1.042. CCDC reference number 779379.

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Table 2 Probing reaction conditions in synthesizing the Baylis-Hillman adducts.

S. no.	Base (eq)[a]	Solvent	Time (h)[b]	Yield (%)[c]
1	DABCO (1.0)	Water	24	90
2	DABCO (1.0)	Dichloromethane	26	92
3	DABCO (1.0)	Methanol	48	55
4	DABCO (1.0)	Tetrahydrofuran	15 days	25
5	DABCO (1.0)	1,4-Dioxane	15 days	20
6	DABCO (1.0)	Neat	4	>94
7	DABCO (0.65)	Neat	4	>94
8	DABCO (0.20)	Neat	8	>94
9	Et_3N (0.65)	Neat	24	[d]
10	Imidazole (0.65)	Neat	24	[d]

[a]2-Chloroquinoline-3-carbaldehyde (1 eq) and methyl acrylate (2 eq) are used; [b]reaction was monitored by TLC; [c]isolated yields; [d]very slow reaction.

2-[(2-Chloro-6,7-dimethoxyquinolin-3-yl)(hydroxy)methyl]-acrylonitrile (5) Yield: 98%; sandy solid; m.p. 118–120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.02 (s, 3H), 5.79 (s, 1H), 6.11 (s, 1H), 6.14 (s, 1H), 7.05 (s, 1H), 7.25 (s, 1H), 7.29 (s, 1H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.8, 55.9, 69.5, 105.8, 106.3, 117.0, 122.6, 124.5, 129.5, 132.7, 135.3, 143.8, 145.2, 150.0, 153.3; IR (KBr): 3535, 3471, 3260, 3108, 2996, 2226, 1621, 1504, 1429, 1249, 1151, 1006, 834 cm^{-1}; MS (ESI): m/z=305 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{15}H_{14}ClN_2O_3$: 305.0692, found: 305.0688.

2-[(2-Chloro-5,8-dimethoxyquinolin-3-yl)(hydroxy)methyl]-acrylonitrile (6) Yield: 95%; light yellow solid; m.p. 156–157°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 3.99 (s, 1H), 5.67 (s, 1H), 6.06 (s, 1H), 6.08 (s, 1H), 6.80 (d, J=8.5 Hz, 1H), 6.99 (d, J=8.5 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.8, 55.8, 69.5, 105.4, 105.5, 109.9, 116.7, 119.7, 124.2, 131.6, 133.1, 133.1, 138.4, 147.2, 147.9; IR (KBr): 3466, 3107, 2963, 2933, 2223, 1620, 1589, 1480, 1323, 1265, 1115, 1061, 809 cm^{-1}; MS (ESI): m/z=305 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{15}H_{14}ClN_2O_3$: 305.0692, found: 305.0698.

2-[(2-Chloro-6-methylquinolin-3-yl)(hydroxy)methyl]acrylonitrile (7) Yield: 97%; creamy solid; m.p. 151–152°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 2.56 (s, 3H), 5.65 (d, J=4.3 Hz, 1H), 6.06 (s, 1H), 6.09 (s, 1H), 6.45 (d, J=4.5 Hz, 1H), 7.56 (dd, J=1.7, 8.6 Hz, 1H), 7.70 (s, 1H), 7.84 (d, J=8.6 Hz, 1H), 8.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 20.6, 69.1, 116.0, 124.4, 126.0, 126.4, 126.7, 130.7, 131.1, 132.2, 135.8, 136.5, 144.8, 146.7; IR (KBr): 3490, 3053, 2938, 2226, 1625, 1591, 1496, 1376, 1339, 1173, 1061, 825 cm^{-1}; MS (ESI): m/z=259 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculate for $C_{14}H_{12}ClN_2O$: 259.0638, found: 259.0648.

2-[(2-Chloro-6-isopropylquinolin-3-yl)(hydroxy)methyl]-acrylonitrile (8) Yield: 97%; creamy solid; m.p. 109–110°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 1.36 (d, J=6.9 Hz, 6H), 3.11 (s, 1H), 5.66 (d, J=4.3 Hz, 1H), 6.05 (s, 1H), 6.07 (s, 1H), 6.36 (d, J=4.7 Hz, 1H), 7.63 (dd, J=1.8, 8.6 Hz, 1H), 7.70 (d, J=1.8 Hz, 1H), 7.89 (d, J=8.6 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 23.4, 33.3, 69.4, 116.6,

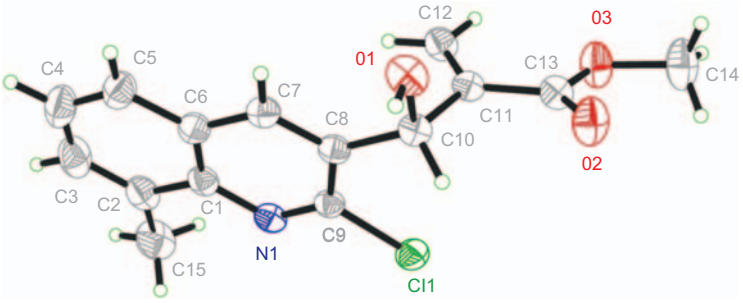

Figure 1 ORTEP diagram of compound **20**.

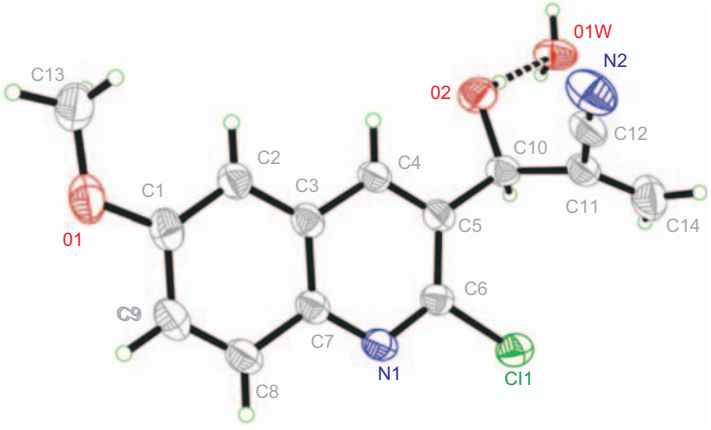

Figure 2 ORTEP diagram of compound **4**.

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Table 3 Antimalarial activity of Baylis-Hillman adducts **2–22** against CQ-sensitive *P. falciparum* strain (FDL-J).

Compound	Inhibitory activity (μg/ml)		Compound	Inhibitory activity (μg/ml)	
	IC_{50}	IC_{90}		IC_{50}	IC_{90}
2	0.80	8.6	**13**	0.38	8.0
3	4.80	19	**14**	4.0	21.5
4	0.15	1.6	**15**	4.2	35
5	0.42	3.3	**16**	0.38	2.5
6	0.52	9.9	**17**	0.35	3.4
7	0.32	1.8	**18**	7.4	51
8	0.58	3.7	**19**	16.5	60
9	0.64	17	**20**	0.15	1.65
10	0.50	3.2	**21**	0.57	12
11	0.13	2.2	**22**	0.16	1.55
12	2.20	9.1	CQ[a]	0.006	0.026

[a]Choloroquine as standard.

124.0, 124.5, 126.8, 127.3, 130.5, 131.9, 132.3, 136.7, 145.4, 147.0, 147.6; IR (KBr): 3201, 2961, 2925, 2229, 1624, 1587, 1497, 1387, 1310, 1178, 1074, 1040, 830 cm^{-1}; MS (ESI): m/z=287 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{16}H_{16}ClN_2O$: 287.0951, found: 287.0942.

2-[(2-Chloro-8-methylquinolin-3-yl)(hydroxy)methyl]acrylonitrile (9) Yield: 98%; creamy solid; m.p. 92–93°C; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 2.74 (s, 3H), 5.67 (d, J=4.5 Hz, 1H), 6.06 (s, 1H), 6.08 (s, 1H), 6.42 (d, J=3.7 Hz, 1H), 7.46 (t, J=6.8 Hz, 1H), 7.57 (d, J=6.8 Hz, 1H), 7.75 (d, J=7.9 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.2, 69.5, 116.7, 124.4, 125.9, 126.8, 127.0, 130.7, 131.8, 132.6, 135.3, 137.4, 145.6, 146.9; IR (KBr): 3461, 2919, 2227, 1592, 1481, 1385, 1329, 1172, 1055, 800, 778 cm^{-1}; MS (ESI): m/z=259 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{14}H_{12}ClN_2O$: 259.0638, found: 259.0627.

2-[(2,7-Dichloroquinolin-3-yl)(hydroxy)methyl]acrylonitrile (10) Yield: 97%; light yellow solid; m.p. 145–146°C; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 5.64 (d, J=4.3 Hz, 1H), 6.08 (s, 1H), 6.11 (s, 1H), 6.52 (m, 1H), 7.56 (dd, J=1.8, 8.8 Hz, 1H), 7.93 (s, 1H), 7.96 (d, J=2.4 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 69.4, 116.5, 124.2, 125.4, 126.2, 127.8, 130.0, 132.6, 133.4, 135.6, 137.1, 146.7, 149.2; IR (KBr): 3205, 2924, 2221, 1611, 1478, 1403, 1339, 1259, 1074, 1038, 809 cm^{-1}; MS (ESI): m/z=279 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{13}H_9Cl_2N_2O$: 279.0091, found: 279.0099.

2-[(2-Chloro-7-fluoroquinolin-3-yl)(hydroxy)methyl]acrylonitrile (11) Yield: 93%; dark brown solid; m.p. 101–102°C; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 5.66 (d, J=4.1 Hz, 1H), 6.05 (s, 1H), 6.09 (s, 1H), 6.41 (d, J=4.3 Hz, 1H), 7.39 (m, 1H), 7.59 (m, 1H), 7.97 (m, 1H), 8.51 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 69.4, 111.1, 111.4, 116.8, 117.5, 117.9, 124.1, 129.8, 129.8, 131.0, 131.1, 131.6, 133.1, 137.3, 147.3, 147.5, 149.2, 161.5, 164.8; IR (KBr): 3483, 3069, 2921, 2224, 1623, 1569, 1491, 1336, 1209, 1122, 1061, 1029, 863, 809 cm^{-1}; MS (ESI): m/z=263 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{13}H_9ClFN_2O$: 263.0387, found: 263.0396.

2-[(2,7-Dichloro-6-fluoroquinolin-3-yl)(hydroxy)methyl]acrylonitrile (12) Yield: 93%; light yellow solid; m.p. 159–120°C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (s, 1H), 6.14 (s, 1H), 6.16 (s, 1H), 7.25 (s, 1H), 7.62 (d, J=6.8 Hz, 1H), 8.11 (d, J=6.8 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 69.4, 113.0, 113.3, 116.8, 123.8, 124.7, 125.0, 126.5, 126.6, 129.3, 133.4, 133.7, 136.8, 136.9, 143.4, 148.5, 148.6, 153.5, 156.8; IR (KBr): 3257, 3065, 2922, 2225, 1598, 1482, 1347, 1226, 1073, 1041, 874, 816 cm^{-1}; MS (ESI): m/z=297 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{13}H_8Cl_2FN_2O$: 296.9997, found: 296.9989.

Methyl 2-[(2-chloroquinolin-3-yl)(hydroxy)methyl]acrylate (13) Yield: 97%; creamy solid; m.p. 124–126°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (d, J=4.9 Hz, 1H), 3.81 (s, 3H), 5.57 (s, 1H), 5.99 (d, J=4.5 Hz, 1H), 6.35 (s, 1H), 7.55 (t, J=7.1 Hz, 1H), 7.71 (t, J=7.1 Hz, 1H), 7.84 (d, J=8.1 Hz, 1H), 8.00 (d, J=8.5 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 69.0, 127.1, 127.2, 127.6, 127.7, 128.0, 130.5, 132.6, 137.0, 140.1, 147.0, 149.2, 166.7; IR (KBr): 3537, 3219, 3060, 2951, 1715, 1625, 1590, 1298, 1145, 1060, 1030, 758 cm^{-1}; MS (ESI): m/z=278 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{14}H_{13}ClNO_3$: 278.0583, found: 278.0592.

Methyl 2-[(2-chloro-7-methylquinolin-3-yl)(hydroxy)methyl]acrylate (14) Yield: 91%; creamy solid; m.p. 95–97°C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3H), 3.18 (s, 1H), 3.71 (s, 1H), 5.73 (s, 1H), 5.94 (s, 1H), 6.34 (s, 1H), 7.37 (d, J=8.1 Hz, 1H), 7.69 (s, 1H), 7.74 (d, J=8.1 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 52.1, 68.8, 125.1, 126.9, 127.3, 127.4, 129.3, 131.8, 136.7, 140.3, 141.1, 147.1, 149.2, 166.6; IR (KBr): 3284, 2948, 2920, 1725, 1624, 1326, 1256, 1133, 1035, 808 cm^{-1}; MS (ESI): m/z=292 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{15}H_{15}ClNO_3$: 292.0740, found: 292.0745.

Methyl 2-[(2-chloro-6-methoxyquinolin-3-yl)(hydroxy)methyl]acrylate (15) Yield: 80%; creamy solid; m.p. 105–106°C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (s, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 5.57 (s, 1H), 5.96 (s, 1H), 6.34 (s, 1H), 7.06 (d, J=1.9 Hz, 1H), 7.33 (dd, J=1.9, 9.7 Hz, 1H), 7.87 (d, J=9.7 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 55.5, 68.9, 105.1, 123.1, 127.5, 128.1, 129.2, 132.8, 135.7, 140.2, 142.8, 146.5, 158.1, 166.6; IR (KBr): 3311, 2956, 2832, 1722, 1624, 1497, 1328, 1257, 1153, 1032, 823 cm^{-1}; MS (ESI): m/z=308 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{15}H_{15}ClNO_4$: 308.0689, found: 308.0695.

Methyl 2-[(2-chloro-6,7-dimethoxyquinolin-3-yl)(hydroxy)methyl]acrylate (16) Yield: 89%; sandy solid; m.p. 133–135°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (d, J=3.0 Hz, 1H), 3.79 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 5.59 (s, 1H), 5.94 (d, J=3.0 Hz, 1H), 6.34 (s, 1H), 7.01 (s, 1H), 7.28 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 56.0, 56.1, 105.0, 106.7, 122.7, 127.3, 130.4, 135.1, 140.3, 144.1, 146.8, 150.0, 153.2, 166.7; IR (KBr): 3391, 3008, 2920, 1713, 1631, 1503, 1247, 1145, 1006, 849 cm^{-1}; MS (ESI): m/z=338 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{16}H_{17}ClNO_5$: 338.0795, found: 338.0791.

Methyl 2-[(2-chloro-5,8-dimethoxyquinolin-3-yl)(hydroxy)methyl]acrylate (17) Yield: 91%; carrot orange solid; m.p. 155–157°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 1H), 3.80 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 5.54 (s, 1H), 6.00 (s, 1H), 6.34 (s, 1H), 6.72 (d, J=8.3 Hz, 1H), 6.92 (d, J=8.3 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 55.6, 55.9, 69.0, 104.3, 108.2, 120.4, 127.5, 132.1, 132.3, 139.0, 140.2, 148.1, 148.5, 149.0,

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166.7; IR (KBr): 3421, 3003, 2934, 1721, 1618, 1475, 1434, 1371, 1266, 1116, 1096, 802 cm^{-1}; MS (ESI): m/z=338 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{16}H_{17}ClNO_5$: 338.0795, found: 338.0782.

Methyl 2-[(2-chloro-6-methylquinolin-3-yl)(hydroxy)methyl]-acrylate (18) Yield: 95%; creamy solid; m.p. 118–119°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.72 (d, J=5.2 Hz, 1H), 3.79 (s, 3H), 5.57 (s, 1H), 5.96 (d, J=4.5 Hz, 1H), 6.34 (s, 1H), 7.51 (dd, J=8.3, 2.2 Hz, 1H), 7.58 (s, 1H), 7.86 (d, J=8.3 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 52.2, 69.2, 126.6, 127.1, 127.6, 127.7, 132.4, 132.8, 136.3, 137.2, 140.1, 145.6, 148.3, 166.7; IR (KBr): 3452, 3000, 2951, 2920, 1699, 1624, 1333, 1257, 1144, 1061, 1035, 821 cm^{-1}; MS (ESI): m/z=292 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{15}H_{15}ClNO_3$: 292.0740, found: 292.0751.

Methyl 2-[(2-chloro-6-isopropylquinolin-3-yl)(hydroxy)meth-yl]acrylate (19) Yield: 90%; semi solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J=6.9 Hz, 6H), 3.09 (s, 1H), 3.46 (d, J=4.7 Hz, 1H), 3.82 (s, 3H), 5.57 (s, 1H), 5.98 (d, J=3.4 Hz, 1H), 6.35 (s, 1H), 7.61 (d, J=8.5 Hz, 1H), 7.63 (s, 1H), 7.92 (d, J=8.5 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 23.8, 34.0, 52.2, 69.2, 123.9, 127.2, 127.6, 127.9, 130.5, 132.3, 136.7, 140.1, 145.9, 148.0, 148.3, 166.8; IR (Neat): 3383, 2960, 1721, 1592, 1495, 1436, 1262, 1145, 1054, 1032, 830 cm^{-1}; MS (ESI): m/z=320 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{17}H_{19}ClNO_3$: 320.1053, found: 320.1061.

Methyl 2-[(2-chloro-8-methylquinolin-3-yl)(hydroxy)methyl]-acrylate (20) Yield: 96%; light yellow solid; m.p. 110–111°C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.7 (d, J=4.8 Hz, 3H), 3.50 (d, J=3.9 Hz, 1H), 3.81 (d, J=6.8 Hz, 3H), 5.58 (s, 1H), 6.00 (s, 1H), 6.35 (d, J=3.9 Hz, 1H), 7.42 (q, J=6.8, 7.8 Hz, 1H), 7.54 (t, J=6.8 Hz, 1H), 7.67 (t, J=8.7 Hz, 1H), 8.31 (d, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 52.1, 68.9, 125.5, 126.8, 127.0, 127.5, 130.4, 132.2, 136.1, 137.0, 140.2, 146.2, 148.1, 166.7; IR (KBr): 3497, 2954, 2922, 1704, 1631, 1436, 1292, 1155, 1084, 1049, 762 cm^{-1}; MS (ESI): m/z=292 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{15}H_{15}ClNO_3$: 292.0740, found: 292.0743.

Crystal data for compound **20**: orthorhombic, space group *Pbca*, a=8.7662 (4) Å, b=14.9431 (7) Å, c=21.3508 (10) Å, α=90 (1)°, β=90 (1)°, γ=90 (1)°, *V*=2796.8 (2) $Å^3$, *Z*=8, D_c=1.386 Mg m^{-3}, μ(Mo Kα) = 0.279 mm^{-1}, F000=1216, *T*=294(2) K. Total number of measured reflections was 25 010. *GOF*=1.087. CCDC reference number 779378.

Methyl 2-[(2,7-dichloroquinolin-3-yl)(hydroxy)methyl]acry-late (21) Yield: 92%; creamy solid; m.p. 102–104°C; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 3.74 (s, 1H), 5.73 (d, J=4.5 Hz, 1H), 5.84 (d, J=4.5 Hz, 1H), 5.95 (d, J=4.9 Hz, 1H), 6.35 (d, J=4.9 Hz, 1H), 7.53 (s, 1H), 7.87 (d, J=4.7 Hz, 1H), 7.94 (s, 1H), 8.32 (d, J=4.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.8, 67.0, 125.5, 126.1, 126.4, 127.9, 130.0, 135.0, 135.1, 136.9, 141.5, 146.4, 150.5, 165.5; IR (KBr): 3433, 2959, 1704, 1613, 1479, 1328, 1260, 1068, 1030, 805 cm^{-1}; MS (ESI): m/z=312 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{14}H_{12}Cl_2NO_3$: 312.0194, found: 312.0203.

Methyl 2-[(2-chloro-7-fluoroquinolin-3-yl)(hydroxy)methyl]-acrylate (22) Yield: 90%; pale yellow solid; m.p. 118–120°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 4H), 5.57 (s, 1H), 5.96 (s, 1H), 6.35 (s, 1H), 7.34 (m, 1H), 7.62 (dd, J=2.2, 9.6 Hz, 1H), 7.84 (m, 1H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 69.1, 112.9, 112.2, 117.5, 117.9, 124.1, 127.7, 129.8, 129.9, 130.3, 132.0, 136.9, 140.0, 147.9, 150.5, 161.9, 165.3, 166.7; IR (KBr): 3537, 3248, 2948, 1714, 1495, 1336, 1209, 1061, 1030, 862, 813 cm^{-1}; MS (ESI): m/z=296 $[M+1]^+$; HRMS: m/z $[M+1]^+$ calculated for $C_{14}H_{12}ClFNO_3$: 296.0489, found: 296.0491.

General procedure for the synthesis of substituted 2-chloroquinoline-3-carboxaldehydes

N,N-Dimethylformamide (0.13 mol) was cooled to 0°C (ice-salt bath) in a round bottom flask and phosphorus oxychloride (0.35 mol) was added dropwise with stirring under nitrogen atmosphere. Acetanilide (0.05 mol) was added to the solution and after 5 min the solution was heated under reflux for appropriate time. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to room temperature and then slowly added to ice-cold water (300 ml), stirred for 30 min at 0–10°C. The precipitated aldehyde was filtered and washed with water (4×50 ml).

Procedure for synthesis of 2-chloro-6-isopropylquinoline-3-carboxaldehyde (1g)

N,N-Dimethylformamide (141.2 mmol, 10.9 ml) was cooled to 0°C in a dry round bottom flask and phosphoryl chloride (396.6 mmol, 36.3 ml) was added dropwise with stirring. To this solution, acetanilide (56.5 mmol, 10 g) was added and after 5 min the solution was heated under reflux at 75°C for 15 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to room temperature and then slowly poured into ice-cold water (300 ml) with constant stirring at 0–10°C. 2-Chloro-6-isopropyl-3-quinoline-carboxaldehyde was filtered off and washed with water. Yield: 81%; creamy solid; m.p. 108–110°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J=6.8 Hz, 6H), 3.11 (J=6.8 Hz, 1H), 7.74 (s, 1H), 7.75 (d, J=8.3 Hz, 1H), 7.98 (d, J=8.3 Hz, 1H), 8.67 (s, 1H), 10.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 33.9, 125.6, 126.1, 126.5, 128.3, 133.6, 139.8, 148.4, 148.9, 149.2, 189.1; IR (KBr): 3047, 2961, 2869, 1695, 1579, 1427, 1376, 1041, 847, 775 cm^{-1}; GC-MS m/z: 233 $[M^+]$.

Biological activity

The anti-*Plasmodium* activity was checked using a well-adapted *P. falciparum* culture line (FDL-J) following the published method (Biswas, 2001). The parasite isolate was collected from a patient reported with symptomatic malaria in a local clinic of Delhi in 2007. The parasite was adapted and maintained *in vitro* by candle-jar technique (Trager and Jensen, 1976). The assay was done in synchronous culture with ring form at 5% haematocrit containing 1% parasitaemia in 96-well flat bottom tissue culture plate. Compounds were dosed in wells in duplicate at concentrations starting from 50 μg/well onwards with five-fold serial dilutions up to 0.0032 μg/well. The volume of culture per well was kept at 200 μl including media, drug and parasite inoculum. The parasite culture only in enriched media was taken as a control. Chloroquine was used as the reference antimalarial for comparison. The assay was done for 48 h to determine the activity of various compounds in total parasite growth. The growth of the parasite in each well was monitored microscopically

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in Giemsa-stained smears by counting the total number of parasites per 5000 red blood cells. Percent parasite growth inhibition was calculated by the formula: (1-Nt/Nc)×100, where Nt and Nc represent the number of parasites in the test and control wells, respectively. Inhibitory concentrations at 50% (IC_{50}) and 90% (IC_{90}) were calculated.

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