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1*H*-1,2,3-Triazole-tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates: Synthesis and antimalarial evaluation

Raghu Raj [a], Jiri Gut [b], Philip J. Rosenthal [b], Vipan Kumar [a,*]

[a] Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, Punjab, India
[b] Department of Medicine, University of California, San Francisco, CA, USA

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ABSTRACT

A series of 1*H*-1,2,3-triazole-tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates have been synthesized and evaluated for their antimalarial activity against chloroquine-resistant W2 strain of *Plasmodium falciparum*. The most potent of the test compound with an optimum combination of 3-hydroxy-indole ring and a *n*-butyl linker displayed an IC_{50} value of 69 nM.

With AIDS and tuberculosis, malaria, caused by the genus *Plasmodium*, is one of the world's deadliest diseases. It is estimated that 216 million people were infected by malaria parasites in 2010, with nearly all of an estimated 700,000 deaths in children infected with *Plasmodium falciparum*.[1] The control of malaria is challenged by lack of an effective vaccine and the development of resistance to most existing antimalarial drugs.[2] Currently, the World Health Organization recommends artemisinin-based combination therapy (ACT), including an artemisinin derivative and a longer-acting partner drug, for the treatment of uncomplicated *falciparum* malaria.[3] However, early signs of artemisinin resistance, manifested as delayed clearance of parasites after therapy in parts of southeast Asia, is of great concern.[4,5] New agents for the treatment and prevention of malaria are greatly needed. Among the existing antimalarial pharmacophores, the 4-aminoquinoline viz. chloroquine (CQ) was the most widely used antimalarial for over 50 years, and the related quinoline, amodiaquine is now widely used as a component of the ACT artesunate-amodiaquine.[6] A number of recent reports have described the synthesis of new 4-aminoquinoline analogues with enhanced activity against CQ resistant (CQR) strains developed via synthetic modifications of CQ side chains.[7–11]

Indoles, especially 1*H*-indole-2,3-dione (isatin) are one of the most prevalent heterocyclic scaffolds found in natural products, pharmaceuticals, and agrochemicals.[12] Many indole derivatives are under development as drug candidates due to their biological properties, which include anti-HIV,[13] antiviral,[14] anti-tumor,[15–17] antifungal,[18,19] anti-angiogenic,[20] anti-convulsant,[21] and anti-parkinsonian activity.[22] The most interesting application of isatin in organic synthesis is based on the highly reactive C-3 carbonyl group, which upon nucleophilic addition or spiro annulation transforms it into 2-oxoindole compounds.[23] In particular, 3-substituted 2-oxoindoles have been used in the synthesis of a range of natural products and have significant biological activities such as progesterone receptor modulation,[24] HIV inhibition,[25] anticancer activity,[26] antimycobacterial activity,[27] and antimalarial activity.[28,29] The indoloquinolines such as cryptolepine (5-methyl-5*H*-indolo[2,3-*c*]quinoline) (I), neocryptolepine (5-methyl-5*H*-indolo[2,3-*b*]quinoline, cryptotackieine) (II), isocryptolepine (5-methyl -5*H*-indolo[3,2-*c*]quinoline, cryptosanguinolentine) (III), and the non-natural isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]quinoline) (IV) have shown potent activity against CQ-resistant strains of *P. falciparum*.[30]

Recently, molecular hybridization has emerged as a useful tool in medicinal chemistry and drug design. The methodology involves the rational design of drugs in which two or more different pharmacophoric units are covalently linked into a single entity to form

* Corresponding author. Tel.: +91 183 2258802x3320; fax: +91 183 2258819 20.
E-mail address: vipan_org@yahoo.com (V. Kumar).

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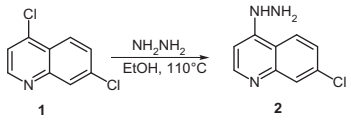
potentially dual-acting compounds.[31,32] The strategy is particularly interesting where treatment is restricted to few drugs or in cases where discovered drugs present pharmacokinetic or pharmacodynamic restrictions.[33]

Our group has recently reported 1*H*-1,2,3-triazole tethered 7-chloroquinoline-isatin conjugates with or without well modulated alkyl chains as potential antiplasmodial agents. Our studies showed dependence of activity on the alkyl chain length and the substituent on the C-5 position of the isatin ring. All hybrids without alkyl chains were inactive, and the compound with the optimum propyl spacer ($n = 3$) and a chloro substituent at the C-5 position of the isatin ring was the most potent of the test compounds, with an IC_{50} for inhibition of development of cultured *P. falciparum* of 1.21 μM.[34] Continuing our efforts to develop biologically relevant conjugates with therapeutic potential,[35] the present work describes the synthesis and antimalarial evaluation of phenolic ether based 1*H*-1,2,3-triazole tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates with well modulated alkyl chain spacers (Fig. 1). Variation in the nature and size of substituents in such molecular frameworks was of interest, as this offers variable electronic, lipophilic, and steric environments that may influence antimalarial activity. The introduction of phenolic ether as linker in these conjugates was based on the recent discovery of small molecule inhibitors of multidrug resistant *P. falciparum* via high throughput luciferase-based assay. The phenolic cluster was shown to constitute more than 50% of the top ChemBridge hits with activities ranging from 36 nM to 15 μM.[36] The inclusion of 1*H*-1,2,3-triazole in the synthesized conjugates was on the basis of its stability under basic, acidic, reductive and oxidative conditions, and additional favourable properties including high dipole moment, capability of hydrogen bonding, and rigidity in the binding of biomolecular targets.[37]

For the synthesis of desired scaffolds, the precursor (7-Chloroquinolin-4-yl)-hydrazine **2** was prepared by refluxing 4,7-dichloroquinoline **1** with hydrazine hydrate in ethanol at 110 °C for 3–4 h (Scheme 1).

The second precursors viz. 1*H*-1,2,3-triazole tethered isatins **6a**–**6l** were prepared by an initial base-assisted alkylation of isatin **3** with dibromoalkanes. The *N*-alkylbromoisatins **4** thus obtained were treated with sodium azide in dry DMF at 60 °C to yield the corresponding *N*-alkylazido-isatins **5** in good yields. Cu-promoted click chemistry of **5** with *O*-propargylated salicyaldehyde led to the isolation of desired precursor **6** with a free aldehydic group in excellent yields (Scheme 2).[38]

The reaction of **2** with **6** in dry chloroform for 5–10 min resulted in the isolation of desired 1*H*-1,2,3-triazole-tethered isatin-7-chloroquinoline conjugates **7** as crude products, which were recrystallized with a chloroform/methanol (95:5) mixture. Treatment of the synthesized Schiff bases **7** with sodium borohydride in methanol resulted in the isolation of 1*H*-1,2,3-triazole tethered 3-hydroxy-indole-7-chloroquinoline conjugates **8** formed by reduction of both (C=N) as well as the isatin keto-carbonyl (Scheme 3). The structure



Scheme 1. Synthesis of (7-Chloro-quinolin-4-yl)-hydrazine **2**.

Table 1
Antimalarial activity of tested compounds

Code	R	n	W2[a] (CQ-R) IC_{50} (nM)	*c*log *P*[b]
6a	H	1	>10,000	1.362
6b	H	2	>10,000	1.684
6c	H	3	>10,000	2.254
6d	F	1	>10,000	1.861
6e	F	2	>10,000	1.685
6f	F	3	>10,000	2.007
6g	Cl	1	>10,000	2.577
6h	Cl	2	>10,000	2.184
6i	Cl	3	>10,000	1.802
6j	CH_3	1	>10,000	2.124
6k	CH_3	2	>10,000	2.694
6l	CH_3	3	6416	2.301
7a	H	1	118	4.791
7b	H	2	165	5.113
7c	H	3	119	5.683
7d	F	1	190	5.290
7e	F	2	288	5.114
7f	F	3	134	5.436
7g	Cl	1	263	6.006
7h	Cl	2	346	5.613
7i	Cl	3	141	5.231
7j	CH_3	1	185	5.553
7k	CH_3	2	163	6.123
7l	CH_3	3	204	5.730
8a	H	1	128	3.412
8b	H	2	339	3.734
8c	H	3	69.0	4.304
8d	F	1	112	3.911
8e	F	2	206	3.735
8f	F	3	164	4.057
8g	Cl	1	182	4.627
8h	Cl	2	350	4.234
8i	Cl	3	168	3.852
8j	CH_3	1	320	4.174
8k	CH_3	2	509	4.744
8l	CH_3	3	326	4.351
Chloroquine			60.0	
Artemisinin			7.00	

[a] CQ-R: Chloroquine resistant.
[b] Calculated using Chem. Draw Ultra 10.0.

of hybrids **7** and **8** were assigned on the basis of spectral data and analytical evidence.[39,40]

The test compounds were evaluated for their antimalarial profiles against the CQ resistant W2 strain of *P. falciparum* (Table 1). The isatin-based triazoles **6a**–**6l** were inactive at tested

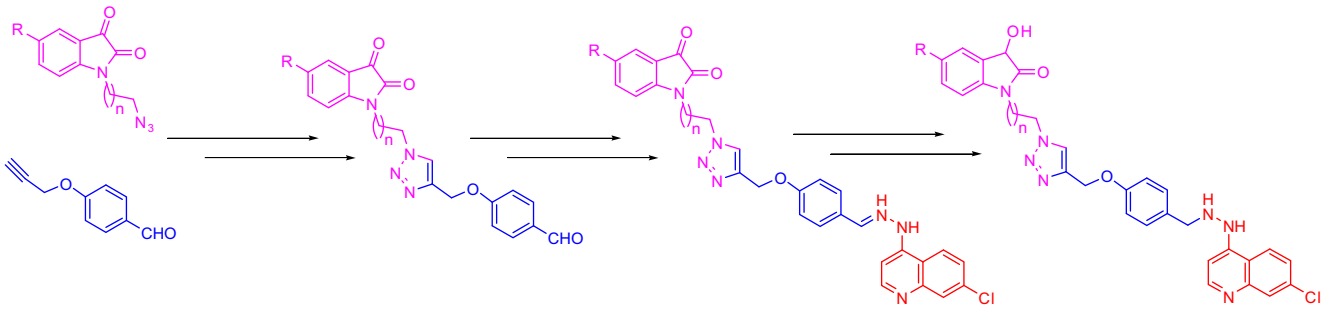
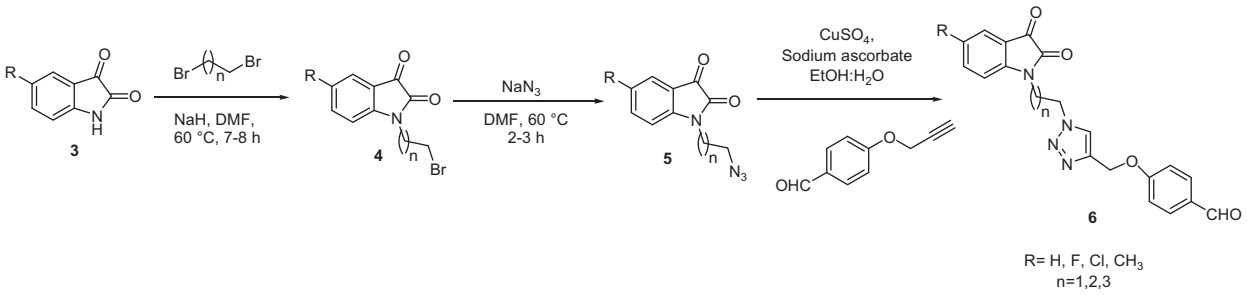
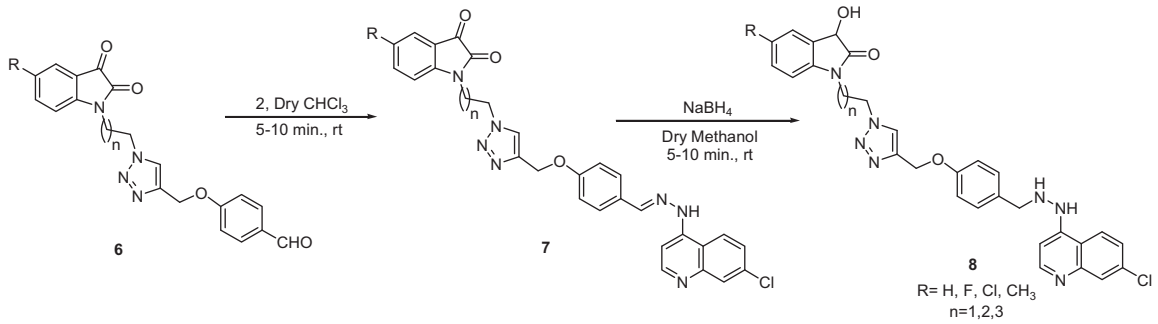


Figure 1. General structure of target hybrid compounds.



Scheme 2. Synthesis of isatin based triazoles **6a–6l**.



Scheme 3. Synthesis of 1*H*-1,2,3-triazole tethered isatin-7-chloroquinoline**7a–7l** and 3-hydroxy indole-7-chloroquinoline conjugates **8a–8l**.

concentrations. The introduction of a 7-chloroquinoline ring markedly improved the antimalarial profiles, as evidenced by the activity of isatin-7-chloroquinoline conjugates **7a–7l** with activity ranging from 118 to 346 nM. The antimalarial profiles of test compounds showed dependence on the length of the alkyl chain introduced as spacers, while the nature of substituents present at the C-5 position of the isatin ring did not appear to influence the activity profiles. Conjugates with even chain lengths viz. $n = 2$ (**7a**, **7d**, **7g**, **7j**) and $n = 4$ (**7c**, **7f**, **7i**, **7l**) were comparatively more potent compared to those with odd chain lengths $n = 3$ (**7b**, **7e**, **7h**, **7k**).

The reduced 3-hydroxy-indole-7-chloroquinoline conjugates viz. **8a–8l** had slightly improved activity compared to isatin-7-chloroquinoline conjugates **7a–7l**, especially in the case of **8c**, **8d**, **8e** and **8g**. Compound **8c**, with an optimum combination of 3-hydroxy-indole ring, butyl linker and reduced imine, showed the best activity among the test compounds, with an IC_{50} value of 69 nM. As evident from Table 1, the introduction of 7-chloroquinoline ring in the tested compounds improved their lipophilicity values calculated by using ChemDraw ultra 10.0. However, the observed antimalarial profiles do not correlate well with the calculated lipophilicity values but most potent of the tested compounds, in general, showed higher lipophilicity values.

In conclusion, the present manuscript describes the synthesis of 1*H*-1,2,3-triazole-tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates along with their antimalarial evaluation against cultured chloroquine-resistant W2 strain of *P. falciparum*. Antiplasmodial activity profiles of tested compounds showed the dependence of activity on the length of alkyl chain but independent of the nature of substituent present at the C-5 position of isatin or indole ring. The synthesized conjugates are not as potent as standard antimalarial drugs (Chloroquine and Artemisinin); however the most potent of the test compound displayed an activity comparable to that of chloroquine, with an IC_{50} value of 69 nM. Further work to improve the activity profiles of 7-chloroquinoline-isatin conjugates via introduction of diverse linkers such as β-aminoalcohol and bis-triazoles is currently underway and will soon be communicated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.12.109.

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38. *Synthesis of 4-{1-[2-(2,3-Dioxo-2,3-dihydro-indol-1-yl)-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-benzaldehyde (**6a**):* To the well stirred solution of 1-(2-Azido-ethyl)-1*H*-indole-2,3-dione (1 mmol) and propargylated *p*-salicyaldehyde (1 mmol) in 30 mL ethanol/water (10:1) mixture was added in succession copper sulphate (0.055 mmol) and sodium ascorbate (0.143 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2–3 h. On completion of the reaction, as monitored by TLC, water (20 mL) was added to the reaction mixture and extracted with chloroform (2 × 50 mL). Organic layers were combined, dried over anhydrous sodium sulphate and concentrated under reduce pressure to result in a crude product which was purified by column chromatography using ethyl acetate/hexane (80:20) mixture to give pure 4-{1-[2-(2,3-Dioxo-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-[1,2,3]triazol-4-ylmethoxy}-benzaldehyde (**6a**). Orange Solid; Yield: 89%; mp 128–129 °C. IR (KBr) ν_{max}: 1737, 1708, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.26 (t, *J* = 5.7Hz, 2H, –*N*–CH_2–); 4.73 (t, *J* = 6.0Hz, 2H, –*N*–CH_2–); 5.20 (s, 2H, –O–CH_2–); 6.56 (d, *J* = 8.1Hz, 1H, ArH); 7.01–7.08 (m, 3H, ArH); 7.40 (t, *J* = 7.8Hz, 1H, ArH); 7.55 (d, *J* = 7.5Hz, 1H, ArH); 7.65 (s, 1H, triazole H); 7.80 (d, *J* = 6.9Hz, 2H, ArH); 9.88 (s, 1H, –CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm = 36.8, 46.9, 61.6, 110.1, 114.7, 117.8, 123.9, 124.1, 125.7, 129.9, 131.8, 138.3, 142.6, 150.1, 157.9, 163.2, 182.5, 191.1. HRMS Calculated for $C_{20}H_{16}N_4O_4$ $[M]^+$ 376.1172 found 376.1163; Anal. Calcd (%) for: C, 63.82; H, 4.28; N, 14.89; Found: C, 63.76; H, 4.38; N, 14.83.
39. *Synthesis of 1-[2-(4-{4-[(7-Chloro-quinolin-4-yl)-hydrazonomethyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-ethyl]-1H-indole-2,3-dione (**7a**):* A mixture of (7-Chloro-quinolin-4-yl)-hydrazine **2** (1 mmol) and **6a** (1 mmol) in dry $CHCl_3$ were stirred at room temperature for 5–10 min. Progress of the reaction was monitored by TLC. The crude product got precipitated out and was recrystallized using chloroform/methanol (95:5) mixture to yield the desired conjugates 1-[2-(4-{4-[(7-Chloro-quinolin-4-yl)-hydrazonomethyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-ethyl]-1*H*-indole-2,3-dione (**7a**). Red Solid; Yield: 85%; mp 178–179 °C. IR (KBr) ν_{max}: 1742, 1612 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.22 (t, *J* = 5.7Hz, 2H, –*N*–CH_2–); 4.79 (t, *J* = 5.7Hz, 2H, –*N*–CH_2–); 5.20 (s, 2H, –O–CH_2–); 6.83 (d, *J* = 7.8Hz, 1H, ArH); 7.05 (t, *J* = 7.5Hz, 1H, ArH); 7.17–7.22 (m, 4H, ArH); 7.53 (dd, *J* = 2.1, 9.0Hz, 1H, H^4, ArH); 7.62 (d, *J* = 1.8Hz, 1H, H^5, ArH); 7.84 (d, *J* = 8.7Hz, 2H, ArH); 7.94 (d, *J* = 7.5Hz, 1H, H^2, ArH); 8.30 (s, 1H, triazole H); 8.43 (d, *J* = 7.5Hz, 1H, H^1,ArH); 8.56 (d, *J* = 9.0Hz, 1H, H^3, ArH); 9.85 (s, 1H, –N═CH–); 12.28 (s, 1H, –NH exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ ppm = 35.6, 45.9, 60.2, 100.2, 108.3, 115.3, 117.4, 120.0, 121.7, 122.1, 124.8, 126.6, 127.9, 129.7, 130.2, 131.8, 136.5, 138.0, 139.4, 141.3, 142.6, 144.2, 149.1, 152.4, 162.6, 164.7, 191.1. HRMS Calculated for $C_{29}H_{22}ClN_7O_3$ $[M]^+$ 551.1473 found 551.1466; Anal. Calcd (%) for: C, 63.10; H, 4.02; N, 17.76; Found: C, 63.03; H, 3.94; N, 17.66.
40. *Synthesis of 1-[2-(4-{4-[N′-(7-Chloro-quinolin-4-yl)-hydrazinomethyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-ethyl]-1H-indole-2,3-dione (**8a**):* To a well stirred solution of **7a** (1 mmol) in dry methanol, sodium borohydride (1 mmol) was added. The reaction mixture was stirred for 5–10 min at room temperature. After completion of the reaction, as monitored by TLC, water (15 mL) was added in reaction mixture and extracted with chloroform (3 × 40 mL). The organic layers were combined, dried over sodium sulphate and concentrated under reduced pressure to result in the isolation of the crude product which after recrystallization using chloroform/methanol (90:10) mixture affords pure product 1-[2-(4-{4-[*N*′-(7-Chloro-quinolin-4-yl)-hydrazinomethyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-ethyl]-1*H*-indole-2,3-dione (**8a**). Red Solid; Yield: 83%; mp 210–211 °C. IR (KBr) ν_{max}: 1629 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.36 (s, 1H, –CH–); 4.21 (t, *J* = 6.0Hz, 2H, –N–CH_2–); 4.42 (d, *J* = 5.7Hz, 2H, –N–CH2); 4.65 (t, *J* = 6.0Hz, 2H, –N–CH_2–); 5.02 (t, *J* = 5.7Hz, 1H, –NH exchangeable with D_2O); 5.09 (s, 2H, –O–CH_2–); 6.92 (d, *J* = 8.4Hz, 2H, ArH); 7.13–7.24 (m, 4H, ArH); 7.41 (t, *J* = 7.5Hz, 1H, ArH); 7.56 (d, *J* = 5.1Hz, 1H, H2, ArH); 7.63 (d, *J* = 7.2Hz, 1H, ArH); 7.69 (dd, *J* = 2.1, 9.0Hz, 1H, H4, ArH); 7.82 (d, *J* = 9.0Hz, 1H, H3, ArH); 7.99 (d, *J* = 2.1Hz, 1H, H5, ArH); 8.22 (s, 1H, triazole H); 8.31 (s, 1H, –OH exchangeable with D2O); 8.80 (d, *J* = 5.1Hz, 1H, H1, ArH); 13.54 (s, 1H, –NH exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ ppm = 36.3, 42.7, 61.1, 62.2, 79.4, 102.2, 109.6, 114.5, 115.1, 119.8, 121.4, 123.1, 124.6, 126.5, 127.7, 128.3, 130.6, 132.8, 134.0, 134.5, 141.4, 142.7, 144.0, 148.9, 152.2, 156.7, 161.9. HRMS Calculated for $C_{29}H_{24}ClN_7O_3$ $[M]^+$ 553.1629 found 553.1637; Anal. Calcd (%) for: C, 62.87; H, 4.37; N, 17.70; Found: C, 62.96; H, 4.44; N, 17.60.