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Synthesis of 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1*H*-β-carbolines as a new class of antimalarial agents

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Abstract—A series of hybrid molecules 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1*H*-β-carbolines have been synthesized and screened for their in vitro antimalarial activity against chloroquine-sensitive strains of *Plasmodium falciparum*. Compounds **26**, **32**, and **34** have shown MIC in the range of 0.05–0.11 μM and are in vitro several folds more active than chloroquine.

Despite over 100 years of drug development efforts, malaria remains one of the most devastating infectious diseases in the world.[1,2] Furthermore, the worldwide burden of malaria is increasing in part due to the spread of resistance to the available anti-malarials especially chloroquine (CQ) and related quinoline-based agents.[3,4] CQ had been the prime therapy for nearly half a century. It was safe, effective, widely available, and remarkably inexpensive and could also be administered to pregnant women and infants, but *P. falciparum*, the cause of the most deadly variety of malaria, is now CQ-resistant (CQ^R) in all epidemic regions of malaria. This rapid spread of resistance has highlighted the need to identify alternative anti-malarials.

Recent approaches are aimed to increase the potency of quinoline-based anti-malarials against the resistant parasite, have included the design and synthesis of quinoline-containing dual inhibitors that would potentially inhibit haemozoin formation and also another target within *P. falciparum*.[5] The 7-chloroquinoline moiety binds to haematin in parasite's acidic food vacuole, thus inhibiting haemozoin formation, and also increases accumulation of the drug due to the protonatable quinoline nitrogen.[6]

Moreover, a number of alkaloids containing a β-carboline moiety, derived from marine sponges, represent important lead structures for the development of anti-infectives.[7–11] Manzamine alkaloids, the most unique group of β-carboline, first isolated in 1986, was found to exhibit significant anticancer activity against P-388 mouse leukemia.[12] More recently, manzamine A has been found to have potent antimalarial activity.[13–15] These β-carbolines interact with DNA through GC-selective intercalation,[16] therefore compounds containing β-carboline moiety can bind to the plasmodial DNA and thereby the inhibition of DNA synthesis of the malarial parasites.

On the basis of these above observations, we have designed and synthesized a class of hybrid molecules consisting of 7-chloroquinoline (haemozoin inhibitor) as a base moiety and tetrahydro-β-carboline moiety (DNA intercalator)-linked diamino alkyl chain at 4-position of 7-chloroquinoline. This letter describes the synthesis and in vitro antimalarial activity of these hybrid molecules.

To synthesize these hybrid molecules (**23**–**45**), compound (**3**) was reacted with different tetrahydro-β-carbolines

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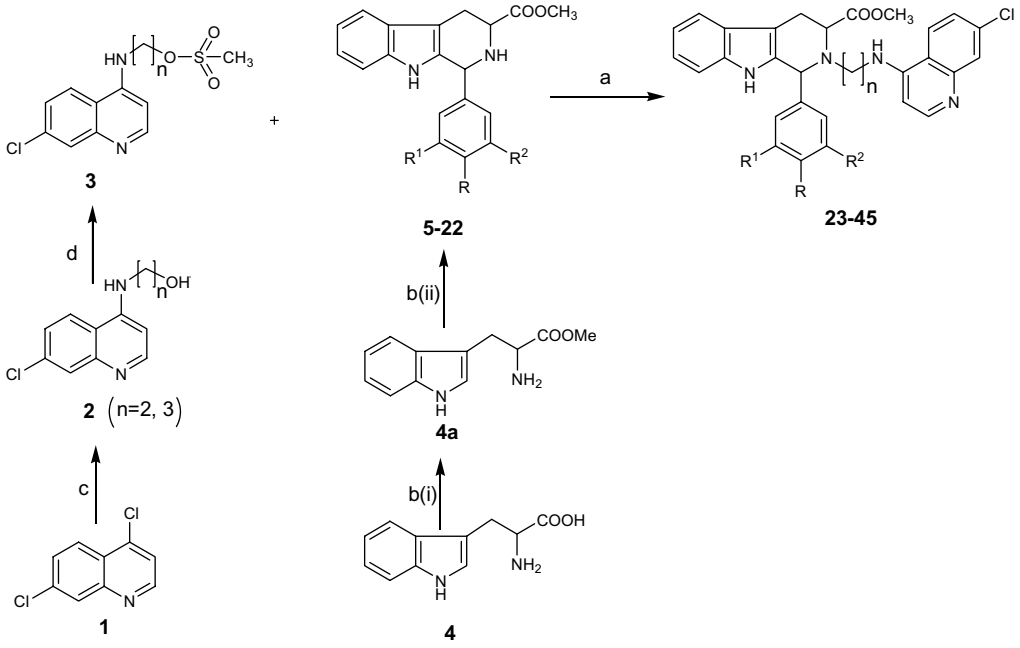
derivatives (**5**– **22**) in DMF at high temperature and pressure. These cis/trans isomers of β-carboline derivatives were prepared by the reaction of D/L tryptophan (**4**) with thionyl chloride in methanol and then the methyl ester (**4a**) was cyclized by Pictet–Spingler cyclization in the presence of different aromatic aldehydes.[17–21] Compound (**3**) was prepared from intermediate (**2**) which was obtained by the reaction of 4,7-dichloroquinoline (**1**) and aminopropanol/aminoethanol in DMF, with methane sulfonylchloride in pyridine at 0 °C.[5,22] (Scheme 1.) All the synthesized compounds were well characterized by spectroscopic methods such as IR, mass, NMR, and elemental analysis.[25]

The in vitro antimalarial assay was carried out in 96-well microtitre plates according to the microassay of Rieckmann et al.[23] 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.[24] The asynchronous parasite of *P. falciparum* was synchronized after 5% D-sorbitol treatment to obtain parasitized cells harboring only the ring stage. For carrying out the assay, an initial ring stage parasitemia of ≈1% at 3% haematocrit in a total volume of 200 μL of medium RPMI-1640 was uniformly maintained. The test compound in 20 μL volume at required concentration (ranging between 0.25 and 50 μg/ml) in duplicate wells was incubated with parasitized cell preparation at 37 °C in a candle jar. After 36–40 h 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 the presence of different concentrations of compounds. The test concentration that inhibits the complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC). Activities of all tested compounds are shown in Table 1.

Among 23 compounds screened against *P. falciparum*, three compounds **26**, **32**, and **34** showed MIC of 0.05, 0.06, and 0.11 μM respectively, whereas three compounds (**23**–**25**) showed MIC of 0.22 μM. On analyzing their biological activity data we found good structure–activity relationship among these compounds. Compounds (**23**–**26**) having isopropyl substitution at *para*-position of phenyl ring and having propyl chain at 2-position of tetrahydro-β-carboline showed MIC in the range 0.05–0.22 μM. While compounds (**27**–**30**) having same isopropyl-substituted phenyl ring, but having ethyl chain showed MIC of 18.12 μM. Similarly compounds **31** and **32** having methyl-substituted phenyl ring and propyl chain at 2-position of tetrahydro-β-carboline, also showed good MIC of 0.46 and 0.05 μM respectively, but compound (**33**) having same methyl-substituted phenyl ring and ethyl chain, showed MIC of 19.08 μM. Compound (**34**) also showed good MIC of 0.11 μM as it has ethyl-substituted phenyl ring and propyl chain at 2-position of tetrahydro-β-carboline. Substituting the phenyl ring with methoxy group at *para*-position the MIC of **35**, **36** and **37** decreases to 3.61 μM and with three methoxy group for **39** and **40**, it goes down to 16.28 μM. Compounds **44** and **45** also showed MIC of 17.54 μM only, as they have thiomethoxy substitution at *para* position of phenyl ring. Substitution of chloro group at *para* position in compounds **42** and **43** showed MIC of 3.58 and 1.79 μM, respectively, while with bromo group (**41**) it decreases to 16.58 μM. If we see the stereochemistry of these compounds we found that compound (**26**) which is prepared from D isomer of tryptophan has MIC of 0.05 μM, while compound (**24**)



Scheme 1. Reagents and conditions: (a) DMF, 120 °C, high pressure; (b) i—$SOCl_2$, MeOH, ii—aromatic aldehydes, reflux; (c) aminoethanol/aminopropanol, Et_3N, DMF, 120 °C; (d) methane sulphonylchloride, Pyridine, 0 °C.

Table 1. Antimalarial in vitro activity against *P. falciparum*

Comp. No.	Isomer	*n*	R	R^1	R^2	MIC (μM)
23	L/cis	3	$-CH(CH_3)_2$	H	H	0.22
24	L/trans	3	$-CH(CH_3)_2$	H	H	0.22
25	D/cis	3	$-CH(CH_3)_2$	H	H	0.22
26	D/trans	3	$-CH(CH_3)_2$	H	H	0.05
27	L/cis	2	$-CH(CH_3)_2$	H	H	18.12
28	L/trans	2	$-CH(CH_3)_2$	H	H	18.12
29	D/cis	2	$-CH(CH_3)_2$	H	H	18.12
30	D/trans	2	$-CH(CH_3)_2$	H	H	18.12
31	L/trans	3	$-CH_3$	H	H	0.46
32	D/trans	3	$-CH_3$	H	H	0.06
33	L/trans	2	$-CH_3$	H	H	19.08
34	D/cis	3	$-CH_2CH_3$	H	H	0.11
35	D/cis	3	–OMe	H	H	3.61
36	D/trans	3	–OMe	H	H	3.61
37	L/cis	3	–OMe	H	H	3.61
38	L/trans	3	–OMe	H	H	18.05
39	L/cis	3	–OMe	–OMe	–OMe	16.28
40	L/trans	3	–OMe	–OMe	–OMe	16.28
41	L/trans	3	–Br	H	H	16.58
42	L/cis	3	–Cl	H	H	3.58
43	L/trans	3	–Cl	H	H	1.79
44	L/cis	3	–SMe	H	H	17.54
45	L/trans	3	–SMe	H	H	17.54
	Chloroquine (standard drug)					0.391

having same substitution at *para* position of phenyl ring but is prepared from L isomer showed MIC of 0.22 μM. Similarly compound (**32**) which is obtained from D isomer has MIC of 0.06 μM and compound (**31**) having same substitution at *para* position of phenyl ring but obtained from L isomer showed MIC of 0.46 μM. Similar results can be seen in case of compounds **36** and **38**. All these results emphasize that compounds obtained from D isomer of tryptophan, having alkylated phenyl ring and propyl chain at 2-position of tetrahydro-β-carboline, are more potent as compared to other molecules.

In conclusion, we have identified 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)- 2,3,4,9-tetrahydro-1*H*-β-carbolines as a novel class of highly potent antimalarial agents. Out of these 23 synthesized compounds, three compounds have shown MIC of 0.22 μM and three have shown MIC in the range of 0.05–0.11 μM which is much more than that of standard drug chloroquine. Therefore these hybrid molecules can be served as new lead in antimalarial chemotherapy.

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25. Spectroscopic data for **24**: Yield 40%; MS: 567 (M+1); mp 161–163 °C; IR (KBr) 3258, 3133, 2910, 2857, 2729, 1752, 1612, 1582, 1491, 1449, 1365, 1329, 1135, 802, 744. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.43 (br s, 1H), 8.35 (d, 1H, J = 7.2 Hz), 8.09 (s, 1H), 7.83 (d, 1H, J = 2.3 Hz), 7.56 (br s, 1H), 7.25 (d, 1H, J = 8.5 Hz), 7.19 to 7.11 (m, 4H), 6.99 (d, 2H, J = 7.6 Hz), 6.85 (d, 2H, J = 8.0 Hz), 6.50 (d, 1H, J = 5.2 Hz), 5.30 (s, 1H), 4.28 (t, 2H, J = 7.0 Hz), 3.65 (s, 3H), 3.58 (dd, 1H, J = 5.0, 5.6 Hz), 3.43 to 3.19 (m, 1H), 2.86 to 2.76(m, 2H), 2.12 (t, 2H, J = 6.2 Hz), 1.73 to 1.59 (m, 2H), 1.31 (d, 6H, J = 7.6 Hz). ^{13}C ($CDCl_3$, 50 MHz): 172.5, 151.8, 150.8, 148.5, 138.1, 137.9, 135.9, 131.2, 128.6, 127.3, 127.0, 125.1, 125.7, 123.8, 121.9, 119.1, 120.0, 118.5, 117.5, 109.5, 108.5, 98.5, 62.7, 56.9, 51.8, 50.4, 43.4, 37.2, 25.5, 24.8, 21.9. Anal. Calcd for $C_{34}H_{35}ClN_4O_2$: Calcd. C: 72.01; H: 6.22; N: 9.88. Found: C: 71.93; H: 6.57; N: 9.74. Spectroscopic data for **26**: Yield 45%; MS: 567 (M+1); mp 163–165 °C; IR (KBr) 3267, 3023, 2925, 2857, 2729, 1744, 1612, 1582, 1491, 1449, 1365, 1329, 1137, 805, 740. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.41 (br s, 1H), 8.36 (d, 1H, J = 6.4 Hz), 8.12 (s, 1H), 7.90 (d, 1H, J = 1.72 Hz), 7.34 (br s, 1H), 7.28 (d, 1H, J = 8.3 Hz), 7.17 to 7.13 (m, 4H), 7.04 (d, 2H, J = 7.8 Hz), 6.83 (d, 2H, J = 8.8 Hz), 6.32 (d, 1H, J = 4.5 Hz), 5.27 (s,1H), 4.18 (t, 2H, J = 7.0 Hz), 3.67 (s, 3H), 3.47 (dd, 1H, J = 5.2, 4.8 Hz), 3.23 to 3.05 (m, 1H), 2.98 to 2.80 (m, 2H), 2.05 (t, 2H, J = 5.3 Hz), 1.64 to 1.58 (m, 2H), 1.23 (d, 6H, J = 8.4 Hz). ^{13}C ($CDCl_3$, 50 MHz): 173.5, 151.8, 150.4, 149.5, 138.1, 137.0, 135.9, 132.5, 129.8, 127.3, 127.1, 126.8, 125.4, 123.3, 122.5, 120.1, 120.0, 118.7, 117.4, 111.5, 108.5, 98.5, 60.7, 56.9, 52.2, 49.4, 43.4, 34.2, 25.7, 24.3, 21.6. Anal. Calcd for $C_{34}H_{35}ClN_4O_2$: Calcd C: 72.01; H: 6.22; N: 9.88. Found: C: 71.58; H: 6.65; N: 8.74.
Spectroscopic data for **32**: Yield 38%; MS: 539 (M+1); mp 164–167 °C; IR (KBr) 3265, 3199, 2930, 2875, 2730, 1784, 1615, 1580, 1491, 1450, 1392, 1364, 1135, 801, 743. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.57 (br s, 1H), 8.29 (d, 1H, J = 7.2 Hz), 8.02 (s, 1H), 7.60 (d, 1H, J = 3.0 Hz), 7.58 (br s, 1H), 7.13(d, 1H, J = 7.5 Hz), 7.01 to 6.98 (m, 4H), 6.82 (d, 2H, J = 6.7 Hz), 6.53 (d, 2H, J = 8.9 Hz), 6.33 (d, 1H, J = 4.0 Hz),5.40 (s, 1H), 4.09 (t, 2H, J = 6.8 Hz), 3.66 (s, 3H), 3.53 (dd, 1H, J = 4.5 and 4.8 Hz), 3.06 to 2.86 (m, 2H), 2.56 (s, 3H), 2.15 (t, 2H, J = 4.0 Hz), 1.63 to 1.59 (m, 2H). ^{13}C ($CDCl_3$, 50 MHz): 172.3, 151.2, 150.5, 138.6, 137.3, 137.0, 135.2, 133.4, 132.5, 129.9, 129.7, 127.1, 125.6, 126.9, 123.3, 122.6, 120.3, 119.9, 118.6, 117.3, 111.5, 108.6, 98.9, 60.5, 56.2, 52.3, 49.3, 43.5, 20.8, 21.7. Anal. Calcd for $C_{32}H_{31}ClN_4O_2$: Calcd C: 71.30; H: 5.80; N: 10.39. Found: C: 70.57; H: 5.65; N: 9.94.
Spectroscopic data for **34**:. Yield 49%; MS: 553 (M+1); mp 170–172 °C; IR (KBr) 3270, 3280, 2930, 2875, 2728, 1764, 1605, 1578, 1490, 1446, 1380, 1355, 1115, 801, 744. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.67 (br s, 1H), 8.49 (d, 1H, J = 7.0 Hz), 8.12 (s, 1H), 7.63 (d, 1H, J = 3.1Hz), 7.50 (br s, 1H), 7.14 (d, 1H, J = 7.5 Hz), 7.05 to 6.89 (m, 4H), 6.72 (d, 2H, J = 6.3 Hz), 6.59 (d, 2H, J = 8.5 Hz), 6.40 (d, 1H, J = 3.6 Hz), 5.31 (s, 1H), 4.09 (t, 2H, J = 6.7 Hz), 3.76 (s, 3H), 3.45 (dd, 1H, J = 5.5, 6.8 Hz), 3.15 to 2.85 (m, 2H), 2.71 to 2.63 (m, 2H), 2.18 (t, 2H, J = 5.7 Hz), 1.75 to 1.53 (m, 2H), 1.31 (t, 3H, J = 5.7Hz). ^{13}C ($CDCl_3$, 50 MHz): 171.9, 152.1, 150.4, 149.5, 139.1, 138.2, 135.5, 132.1, 130.3, 128.9, 128.8, 127.5, 125.4, 122.9, 122.2, 122.6, 119.9, 118.5, 118.3, 116.5, 111.8, 101.6, 98.8, 61.2, 57.1, 53.2, 50.0, 43.5, 27.5, 25.9, 22.8, 17.2. Anal. Calcd for $C_{33}H_{33}ClN_4O_2$: Calcd C: 71.66; H: 6.01; N: 10.13. Found: C: 69.87; H: 6.15; N: 10.01.
Spectroscopic data for **43**: Yield 37%; MS: 559 (M+1); mp 179–182 °C; IR (KBr) 3190, 3250, 2928, 2869, 2638, 1759, 1615, 1498, 1490, 1437, 1380, 1367, 1095, 798, 756. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.52 (br s, 1H), 8.30 (d, 1H, J = 6.9 Hz), 8.05 (s, 1H), 7.75 (d, 1H, J = 2.7Hz), 7.38 (br s, 1H), 7.10 (d, 1H, J = 8.0Hz), 7.15 to 7.11 (m, 4H), 6.99 (d, 2H, J = 7.6 Hz), 6.72 (d, 2H, J = 7.8 Hz), 6.45 (d, 1H, J = 3.5 Hz), 5.39 (s, 1H), 4.13 (t, 2H, J = 6.8 Hz), 3.72 (s, 3H), 3.65 (dd, 1H, J = 4.0, 4.3 Hz), 3.10 to 2.99 (m, 2H), 2.12 (t, 2H, J = 5.2 Hz), 1.72 to 1.65 (m, 2H). ^{13}C ($CDCl_3$, 50 MHz): 172.52, 150.9, 150.4, 148.2, 137.2, 137.0, 135.5, 131.2, 128.8, 127.5, 127.2, 126.8, 124.6, 123.3, 122.6, 121.1, 121.0, 118.7, 116.9, 110.3, 108.6, 98.6, 61.2, 57.1, 50.9, 50.1, 43.2, 26.2, 21.7. Anal. Calcd for $C_{31}H_{28}Cl_2N_4O_2$: Calcd C: 66.55; H: 5.04; N: 10.01. Found: C: 69.87; H: 5.15; N: 9.08.