New Chloroquine Derivatives: Synthesis, Characterisation, Antiplasmodial and Antioxidant Evaluations

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Research Article

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Abstract

Quinoline is a privileged pharmacophore in many bioactive compounds possessing antimalarial activity. In this paper, some novel 4-aminoquinoline derivatives were synthesized in good yields in order to investigate their antimalarial and antioxidant properties. This was achieved by combining N⁴-(7-chloroquinolin-4-yl)propane-1,3-diamine **7** with various boc-amino acids. Amongst the synthesized derivatives, *tert*-buty(1-((3-((7-chloroquinolin-4- yl)amino)propyl)amino)-4-methyl-1-oxopenta-2-yl)carbamate **(**IC50 = 1.11 mg/mL) and *tert*- butyl 2-((3-((7-chloroquinolin-4-yl)amino)propyl)carbamoyl)pyrrolidine-1-carboxylate **(**IC50 = 1.30 mg/mL) exhibit relatively better antiplasmodial activities compared to chloroquine diphosphate (IC50 = 0.84 mg/mL). In addition, *tert*-butyl(2-((3-((7-chloroquinolin-4- yl)amino)propyl)amino)-2-oxoethyl)carbamate exhibited better antioxidant activity (IC50 = 0.48 mg/mL) than ascorbic acid (IC50 = 0.41 mg/mL).

1 INTRODUCTION

The threat posed by malaria, an infectious parasite illness, affects around half of the global population. The female Anopheles mosquito that consumes blood spreads this parasitic disease. Children and pregnant people are especially prone to contracting malaria in subtropical areas. Globally, there will likely be 241 million cases of malaria and 627,000 malaria-related fatalities in 2020, according to the most recent WHO World Malaria Report. This amounts to an extra 69,000 deaths and an additional 14 million cases in 2020 when compared to 2019 [1]. There are five parasites in the genus *Plasmodium* that cause malaria, but *Plasmodium falciparum* and *Plasmodium vivax* are the most deadly [2,3,4].

Effective drugs have been developed to treat malaria and a good example of such drugs are quinine, chloroquinoline, mefloquine and artemesinin. All these drugs have quinoline moiety except artemisinin. Chloroquine (CQ) has been a choice antimalarial drug in the 1940s because it was a cheap and easily available drug to patient. In addition because of its low toxicity it was a frontline drug for treatment of malaria in children and pregnant women. However, its efficacy was compromised by parasitic resistant and it clinical usage has since been restricted in many countries, including Nigeria [5]. Therefore intentional research effort had been on to functionalize chloroquine motif in order to develop drug that may possess all the advantages of chloroquine and to overcome CQ resistant parasite strains.

Studies have shown that altering the 7 chloroquinoline ring's structure in chloroquine decreases its antimalarial activity, but changing the side chain of chloroquine seems to be more effective [6,7]. *In vitro* and *in vivo* studies using chloroquine analogs with branched and linear side chains and two or three methylene groups between the amino groups against a chloroquine-susceptible (CQS) strain of *Plasmodium falciparum* revealed that they were more effective than chloroquine against the chloroquine-resistant strain (CQR) [8,9].

Increased oxygen free radical production and decreased levels of antioxidant enzymes are linked to the physiopathogenesis of malaria [10,11]. *P. falciparum* breaks down hemoglobin inside the host RBCs, resulting in the creation of heme. This heme then triggers the production of reactive oxygen specie, which

causes anemia and oxidative stress-related apoptosis [12,13,14]. Stress results in molecular and cellular damage, which is connected to a number of diseases include cancer, bacterial infections and aging. Therefore, in the development of antimalarial drugs, drug with antiplasmodial activity that can scavenge oxygen free radicals are greatly desired.

Numerous studies have shown that the majority of commercially available drugs cause pathogenic microorganisms to become resistant to them. The problem is aggravated due to the emergence of new pathogenic microorganism. In addition, free radicals also attack body's cells causing deleterious disease. Antioxidants are substances that provide their own electrons to these damaged cells in order to prevent and stabilize the damaged caused by free radicals. It also turns free radicals into waste by- products, which are eliminated from the body [15].

In our quest for antiplasmodial compounds in the 4-aminoquinoline derivatives, the synthesis, *in vitro* antiplasmodial and antioxidant activities of five new 4-aminoquinoline analogues were described.

2 RESULTS AND DISCUSSION

Refluxing of 4,7-dichloroquinoline with excess 1,3-diaminopropane under neat condition for 10 h gave N'-(7-chloroquinolin-4-yl)propane-1,3-diamine as intermediate product after work-up, melting at 180 ^{o}C, to 200 ^{o}C. The reaction occurred by nucleophile substitution of amino group of 1,3-diaminopropane with chloro group of 4,7-dichloroquinoline to afford the intermediate as yellow product. The N'-(7-chloroquinolin-4-yl)propane-1,3-diamine was further coupled with various boc-amino acids in the presence of DCC/HOBt as coupling reagent to afford variety of boc amino substituted 7-chloroquinoline analogs. The reaction was simply carried out by stirring the boc-amino acid and the intermediate in DCM at room temperature for 3h until the completion of the reaction's at the end of the reaction, excess dicyclohexylurea (DCU) was eliminated after the reaction by washing with 10% NaHCO3 (3 x 50 ml) and brine solution.
Alternatively, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) may also be used in place of DCC because it is water soluble and result product can easily be isolated by solvent extraction. In this work, DCC was employed to activate the carboxyl group of the amino acid instead of EDC.HCl because it is cheaper in spite of its setback in forming inactive *N*-acylurea. However, using DCC and 1-hydroxylbenzotriazole (HOBT), the protonation of O-acylurea into *N*-acylurea at low temperature was mitigated.

3.1 Biological activity

The synthesized compounds were evaluated for antiplasmodial and antioxidant activities with chloroquine diphosphate and ascorbic acid employed as reference standards respectively. The structural variation in R group lead to changes in the activities of the analogs. Tables 1 and 2 shows the results of the biological activity investigations.

3.1.1 *In Vitro* Antiplasmodial Activity:

The five compounds synthesized were tested *in-vitro* for antiplasmodial activities using chloroquine diphosphate as the standard. The half maximum inhibitory concentration (IC50) values for the synthesized analog were given in 1. All the five synthesized 7-chloroquine derivative exhibited antiplasmodial activities although none of them were as active as chloroquine disphosphate used as the standard. The compounds 1a and 1e containing boc-alanine and boc- glycine moieties exhibited poor activities. The derivatives incorporating boc-leucine (id), boc- proline (1c) and boc-phenylalanine (1b) in their molecular structures showed enhanced activities.

Table 1
Half maximal inhibitory concentration of compound 1a-1e for antiplasmodial activities

Concentration	Chloroquine diphosphate	Compound 1a	Compound 1b	Compound 1c	Compound 1d	Compound 1e
5 mg/mL	87	51	11.9	35	20.6	58
2 mg/mL	79	48	12	34	19.1	47
1.25 mg/mL	80	37	11	33	30.1	46
0.625 mg/mL	75	39	8.5	28	16.2	51
IC50	0.84	2.35	1.72	1.11	1.30	5.68

Compound **1b** and **1c** with branch and alicyclic R group lead to increase in antimalarial activities than compound **1a** and **1e** where R groups are –CH and -H. Compound **1b** where R = -CH2C6H5 showed moderate activity compare to the other analogs. Overall, it was observed that compound **1c** (1.11 mg/mL) demonstrated higher activity compared to other compounds and this may be attributed to the branched carbon chain.

3.1.2 In Vitro Antioxidant Activity:

The DPPH radical scavenging ability of the newly synthesized chloroquine derivatives were relatively moderate. Compounds **1b, 1c** and **1d** gave maximal inhibitory concentration (IC50) range 0.4100–2.984 mg/mL. The percentage free radical inhibition of compound 1a where R= - CH3 and **1e** where R = H were generally low compared to other derivatives with R being a group with higher molecular masses. Compound **1b** where R = isopropyl group and **1c** where R = Pyrrolidine group exhibit enhanced and comparable activity compared to ascorbic acid (0.41 mg/mL).

Table 2
Half maximal inhibitory concentration of compound 1a-1e for antioxidant activities

Concentration	Ascorbic acid	Compound 1a	Compound 1b	Compound 1c	Compound 1d	Compound 1e
5 mg/mL	80.6	79	38	12.64	67.9	75
2 mg/mL	82.4	82	46	41.33	74	81
1.25 mg/mL	79.1	77	31	41.21	66	80
0.625 mg/mL	81.9	80.34	72	57.7	81	87.5
IC50	0.41	1.774	0.545	2.980	0.484	1.25

It is worthy to note that compound **1d** elicited the highest activity and this may be attributed to the presence of heterocyclic pyrollidine ring in the molecule. In general compound **1b** and **1d** recorded both good antiplasmodial and antioxidant activities.

Table 3
Binding energy of the compounds

Target	Native ligand	Compound 1a	Compound 1b	Compound 1c	Compound 1d	Compound 1e
3qs1	-9.46	-7.02	-7.55	-7.35	-6.64	-6.76
2x08	-4.57	-7.70	-7.12	-6.10	-7.01	-6.98

We undertook molecular docking studies to gain further insight into the interactions of the synthesized compounds and the antioxidant and antimalarial drug targets. The results in Table 3 show that the synthesized compounds had strong binding affinity and interacted favorably with the active binding sites of the proteins. Inhibiting the biochemical activities of these proteins is possible according to our compound's strong binding affinities 16. Compound 1a gave the highest antioxidant activity (– 7.70 kcal/mol). This corroborated well with the antioxidant result in Table 2. The binding modes of the compounds 1a and 1b with the drug targets 2X08 and 3QS1 respectively, including their 2D interactions with the amino acid residues of the targets are shown in Fig. 2. These compounds showed good fitting into the active binding sites of the targets. Figure 2(d) showed that compound 1a (green colour) effectively interacted with the same key amino acids as the ascorbic acid (native ligand – red coloured). GLY 41, ASP 37 and ARG 184 played key roles. This could explain the high binding affinity that compound 1a has with 2X08. 1a could be a potential anti-oxidant agent.

4 CONCLUSION

The successful synthesis of some chloroquine derivatives bearing variety of boc-amino acids was achieved in good yields. The *in vitro* antiplasmodial and antioxidant investigation indicated that compounds Ib and 1d incorporating benzyl and pyrrolidine moieties respectively show good activities. The

molecular docking studies confirmed the compounds were inhibitors of 3QS1 and 2X08 protein drug targets. Hence, compounds 1b and 1d are worthy of further study because of distinct dual antiplasmodial and antioxidant activities.

5 EXPERIMENTAL SECTION

General Information

All the chemicals and reagents used in the synthesis of new chloroquine derivatives were of synthetic grade obtained from Sigma-Aldrich chemical company, UK. The syntheses were conducted in the Postgraduate Research Chemistry Laboratory, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka. The IR spectra were carried out at Nnamdi Azikiwe University, Awka and were recorded using Shimadzu FTIR- 8400s Fourier Transform Infrared (KBr pellets) respectively. Nuclear Magnetic Resonance (^{1}HNMR and ^{13}CNMR) spectra were determined using a Bruker AV-400 spectrometer at Rhodes University, South Africa. Chemical shifts were recorded on the δ-scale (neat) and coupling *J* constant reported in hertz (Hz). Multiplicity were reported with the following abbreviations: d for doublet, dd for doublet of doublet, t for triplet and m for multiplet. Antimicrobial screening was done at the Department of Pharmacology, Faculty of Pharmacy, University of Nigeria, Nsukka.

5.1 Procedure for the synthesis of intermediate

To 4,7–dichloroquinoline (1.0 equiv) was added to 1,3-diaminopropane (12.0 equiv). The reaction was run neat at reflux for 10 h. The bulk of excess propane-1,3-diamine was evaporated under heat and vacuum. The remaining waxy solid was suspended in 200 mL water, and stirred for 20 min. The solid suspension was filtered to leave a pure white product.Yield 3.21g (91%), FTIR (KBr, cm^{-1}): 2713.724, 2886.18, 3109.68 (C-H, stretch), 3394.78, 3669.28, 3828.42 (N-H, stretch), 1372.41 (C-N).^{1}H NMR (400 MHz, CDCl3) δ ppm: 6.39 – 8.9 (m, 5H, Ar-H), 8.25 (s, 1H, NH), 7.2 (s, 2H, NH), 3.35 (m, 2H, CH2), 3.25(m, 2H, CH2), 1.75(m, 2H, CH2).^{13}C NMR (400 MHz, CDCl3) δ ppm: 140.13, 139.04, 128.15, 127.33, 125.26, 124.50, 120.95, 118.21, 97.59 (Aromatic carbon), 49.16, 36.00, 33.91 (Aliphatic carbon).

5.2 General procedure for the synthesis of compound 1a-e

To a stirred solution of Boc-protected amino acids (5 mmol, 1 equiv) in dry DCM (20 mL) was added DCC (7.5 mmol, 1.5 equiv) dissolved in 5 mL of DCM and HOBt (6 mmol, 1.2 equiv) dissolved in 2 mL of DMF at 0 °C. After 5 min, N-(7-chloroquinolin-4-yl)propane-1,3-diamine was added slowly to the stirred reaction mixture. After the reaction mixture had been stirred for an 1 h at room temperature, it was allowed to warm up to room temperature for 30 min. Following the TLC- indicated completion of the reaction, the precipitated dicyclohexylurea (DCU) was extracted by filtration, and the filtrate was then washed with 10% aqueous $NaHCO_3$ (3 X 50 mL) and 10% aqueous citric acid (3 x 50 mL) solution before final wash with a brine solution.

The organic layer was dried over anhydrous Na2SO4 and evaporated to a gummy residue. The residue was allowed to cool for 2 h at 0 °C after being dissolved in a minimum amount of THF. The residual DCU was precipitated and filtered at this time. An amide was obtained by evaporating the filtrate.

5.2.1 *tert*-buty(1-((3-((7-chloroquinolin-4-yl)amino)propyl)amino)-1-oxopropan-2-yl)carbamate (1a):

Yield 0.23g (51%). FTIR (KBr, cm^{-1}): 2718.38, 2824.56, 3077.87 (C-H, sp^3), 1618.72 (C=C, ring), 1947 (C=O), 1372.41 (C-N), 3372.52, 3678.81, 3829.98 (N –H), 816.28 (C-Cl).^{1}H NMR (400 MHz, CDCl3) δ ppm: 6.39 – 8.9 (m, 5H, Ar-H), 8.25 (s, 1H, NH), 7.2 (s, 1H, NH), 7.1(s, 1H, NH), 4.35 (t, 1H, CH-CH2), 3.35 (m, 2H, CH2), 3.25(m, 2H, CH2), 1.75(m, 2H, CH2), 1.5 (d, 3H, CH-CH3), 1.3 (s, 9H, C-CH3). ^{13}C NMR (400 MHz, CDCl3) δ ppm: 173.55 -174.85 (C=O), 140.13, 139.04, 128.15, 127.33, 125.26, 124.50, 120.95, 118.21, 97.59 (Aromatic carbon), 80.08, 49.16, 36.00, 33.91, 28.28, 27.70 (Aliphatic carbon).

5.2.2 *tert*-buty(1-((3-((7-chloroquinolin-4 yl)amino)propyl)amino)-1-oxo-3-phenylpropan-2- yl)glycinate (1b)

Yield 1.0 g (54%), FTIR (KBr, cm^{-1}): 2610.3, 2849.19, 2954.83 (C-H, sp^3), 1633.33 (C=C, ring), 1958.08 (C=O), 1396.71 (C-N), 3083.3, 3214.08, 3806.76 (N-H), 761 (C-Cl).^{1}H NMR (400 MHz) δ ppm: 7.65 – 8.6 (m, 10H, Ar-H), 7.4 (s, 1H, NH), 7.35 (s, 1H, NH), 7.2 (s, 1H, NH), 4.45 (t, 1H, CH-CH2), 3.35 (m, 2H, CH2), 3.25(m, 2H, CH2), 3.1(d, 2H, CH2-CH), 1.75(m, 2H, CH2), 1.4(s, 9H, C-CH3). ^{13}C NMR (400 MHz, CDCl3) δ ppm: 171.82 – 173.04 (C=O), 155.41, 142.38, 139.58, 139.19, 136.71, 129.31,128.69, 128.61, 128.55, 127.74, 127.08, 126.89, 115.80, 97.50 (Aromatic carbon), 80.16, 49.17, 35.80, 33.91, 28.29, 25.60, 24.94 (Aliphatic carbon).

5.2.3 *tert*-buty(1-((3-((7-chloroquinolin-4-yl)amino)propyl)amino)-4-methyl-1-oxopenta-2- yl)carbamate (1c)

Yield 1.08 g (56%), FT-IR (KBr, cm^{-1}): 2629.17, 2951.19, 3230.72 (C-H, sp^3), 1620.91 (C=C, ring), 1885.25 (C=O), 1434.306 (C-N), 3424.23, 3541.06, 3826.63 (N-H), 758.98 (C-Cl).^{1}H NMR (400 MHz, CDCl3) δ ppm: 7.8 – 9.4 (m, 5H, Ar-H), 7.7 (s, 1H, NH), 7.6 (s, 1H, NH), 7.35 (s, 1H, NH), 4.3 (t, 1H, CH-CH2), 3.4 (m, 2H, CH2), 3.0 (m, 2H, CH2), 1.7 (m, 2H, CH2), 1.6 (t, 2H, CH-CH2-CH), 1.3 (m, 1H, CH2-CH-CH2), 1.15 (s, 9H, C-CH3), 0.85 (m, 6H, CH-CH3). ^{13}C NMR (400 MHz, CDCl3) δ ppm: 173.51 – 174.77 (C=O), 155.90, 155.65, 142.02, 139.74, 138.80, 127.81, 125.17, 119.78, 97.55 (Aromatic carbon), 80.01, 53.54, 41.08, 40.06, 35.87, 28.32, 28.30, 24.61, (Aliphatic carbon).

5.2.4 *tert*-butyl 2-((3-((7-chloroquinolin-4-yl)amino)propyl)carbamoyl)pyrrolidine-1-carboxylate (1d)

Yield 1.10 g (55%), FT-IR (KBr, cm^{-1}): 2718.38, 2824.56, 3077 (C-H, sp^3), 1619.72 (C=C, ring), 1842.58 (C=O), 1388.76 (C-N), 3372.52, 3676.8, 3829.98 (N-H), 816 (C-Cl).^{1}H NMR (400 MHz, CDCl3) δ ppm: 8.1 – 9.35 (m, 5H, Ar-H), 7.8 (s, 1H, NH), 7.3 (s, 1H, NH), 3.4 (m, 2H, CH2), 3.35 (m, 2H, CH2), 3.25 (t, 1H, CH-CH2), 1.75(m, 2H, CH2), 1.6 (m, 6H, pyrollidine-H), 1.1 (s, 9H, C- CH3). ^{13}C NMR (400 MHz, CDCl3) δ ppm: 173.51 – 174.77 (C=O), 155.53, 139.71,138.52,136.7, 133.6, 127.78, 125.32, 119.96, 96.5 (Aromatic carbon), 80.54, 49.24, 33.83, 28.41, 25.56, 24.90 (Aliphatic carbon).

5.2.5 *tert*-butyl(2-((3-((7-chloroquinolin-4-yl)amino)propyl)amino)-2-oxoethyl)carbamate (1e)

Yield 0.85 g (50%), FTIR (KBr, cm^{-1}): 3018 (C-H, sp^3), 1485 (C=C, ring), 1740 (C=O), 1245 (C-N), 3280 (N-H), 752 (C-Cl).^{1}H NMR (400 MHz, CDCl3) δppm: 6.9 – 7.9 (m, 5H, Ar-H), 7.6 (s, 1H, NH), 7.4 (s, 1H, NH), 7.2 (s, 1H, NH), 3.95 (s, 2H, CH2), 3.35 (m, 2H, CH2), 3.2 (m, 2H, CH2), 1.8 (m, 2H, CH2), 1.1 (s, 9H, C-CH3). ^{13}C NMR (400 MHz, CDCl3) δ ppm: 173.51 – 174.77 (C=O), 155.90, 155.65, 142.02, 139.74, 138.80, 127.81, 125.17, 119.78, 97.55 (Aromatic carbon), 80.1, 49.35, 33.82, 30.94, 28.32, 25.56 (Aliphatic carbon).

6 Molecular docking studies

The drug targets used for antioxidant and antimicrobial activities of our compounds were cytochrome C peroxidase (PDB code: 2X08) and plasmepsin I (PMI) from Plasmodium falciparum (PDB code: 3QS1) respectively. Protein data was used to obtain the 3D structures of these drugs (http://www.rcsb.org). The protein was prepared in Discovery Studio and the unwanted multiple chains and water of crystallization was removed. The prepared proteins and the synthesized compounds were loaded into Molecular Operating Environment and energy minimized using Force field MMFF94X. Using the MOE docking program, the binding of the ligand molecule to the protein molecule was examined to determine the proper conformation.

Declarations

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contribution

chukwuebuka festus carried out the research and wrote the manuscript. Dr. Onoabedje and Prof. Benjamin designed the research work. Dr. Sunday did the molecular docking and Miss Ezeugwu Joy assisted in the synthesis

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

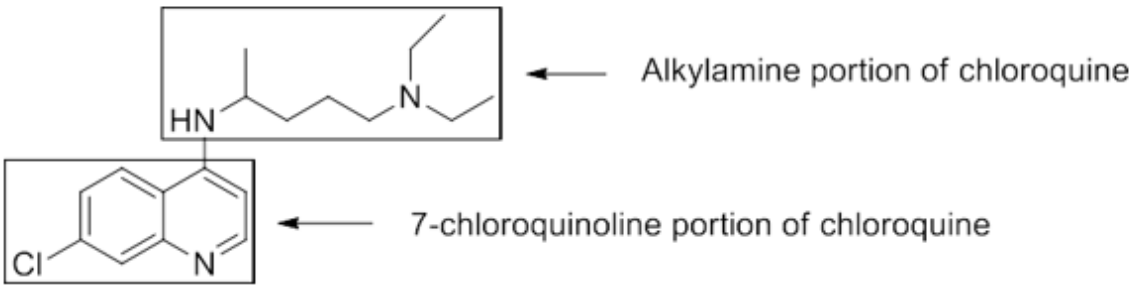

Figure 1

Chloroquine

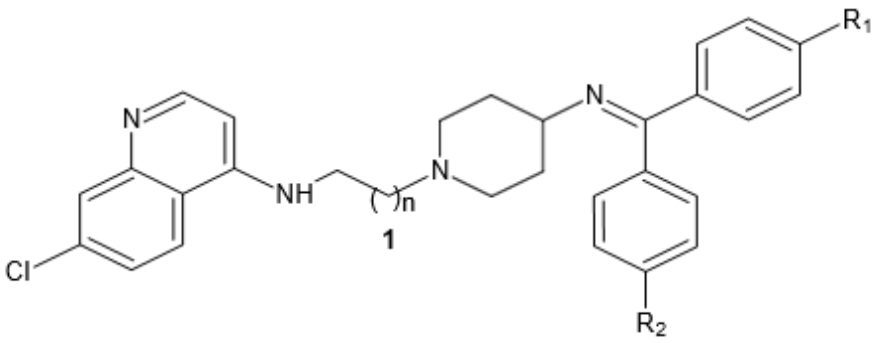

Figure 2

designed chloroquine derivative

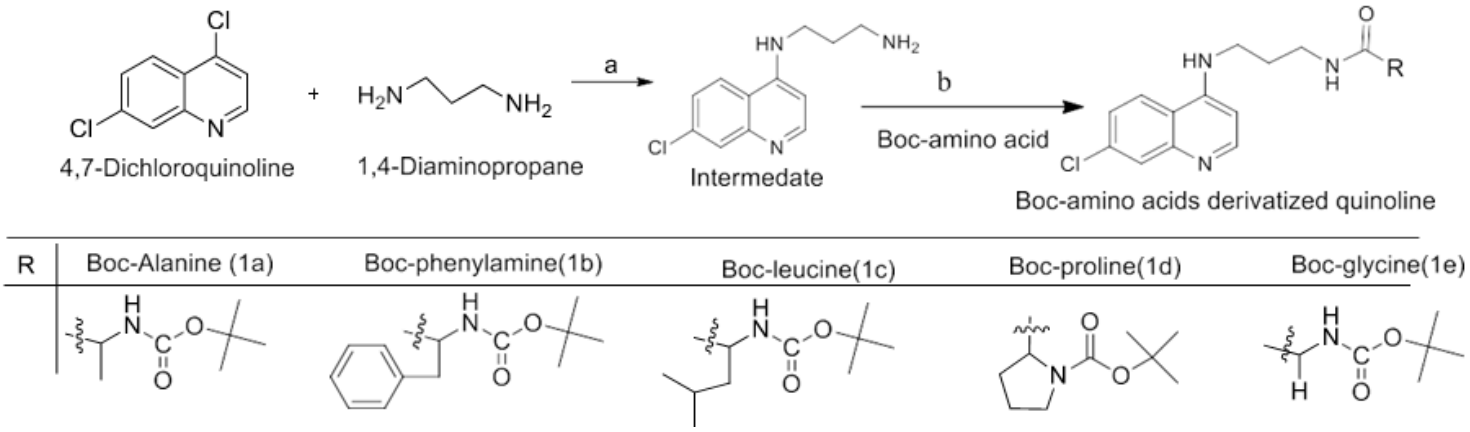

Figure 3

Reagent and conditions: (a) Reflux for 10 h, 120 ^{o}C ; (b) Room temperature, Boc-amino acid (5.0 mmol), dichloromethane (DCM), N, N'-dicyclohexylcarbodimide (DCC) (1.5 equiv), hydroxybenzotriazole (HOBt) (1.2 equiv in 2 mL of dimethylformaldehyde (DMF)

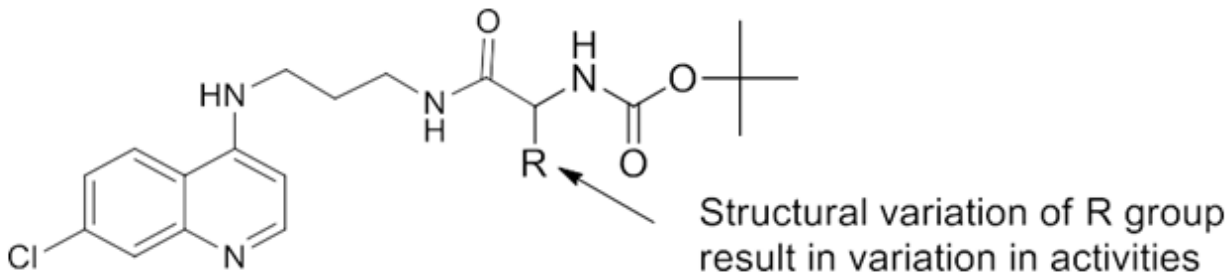

Figure 4

Boc-amino acids derivatized quinoline

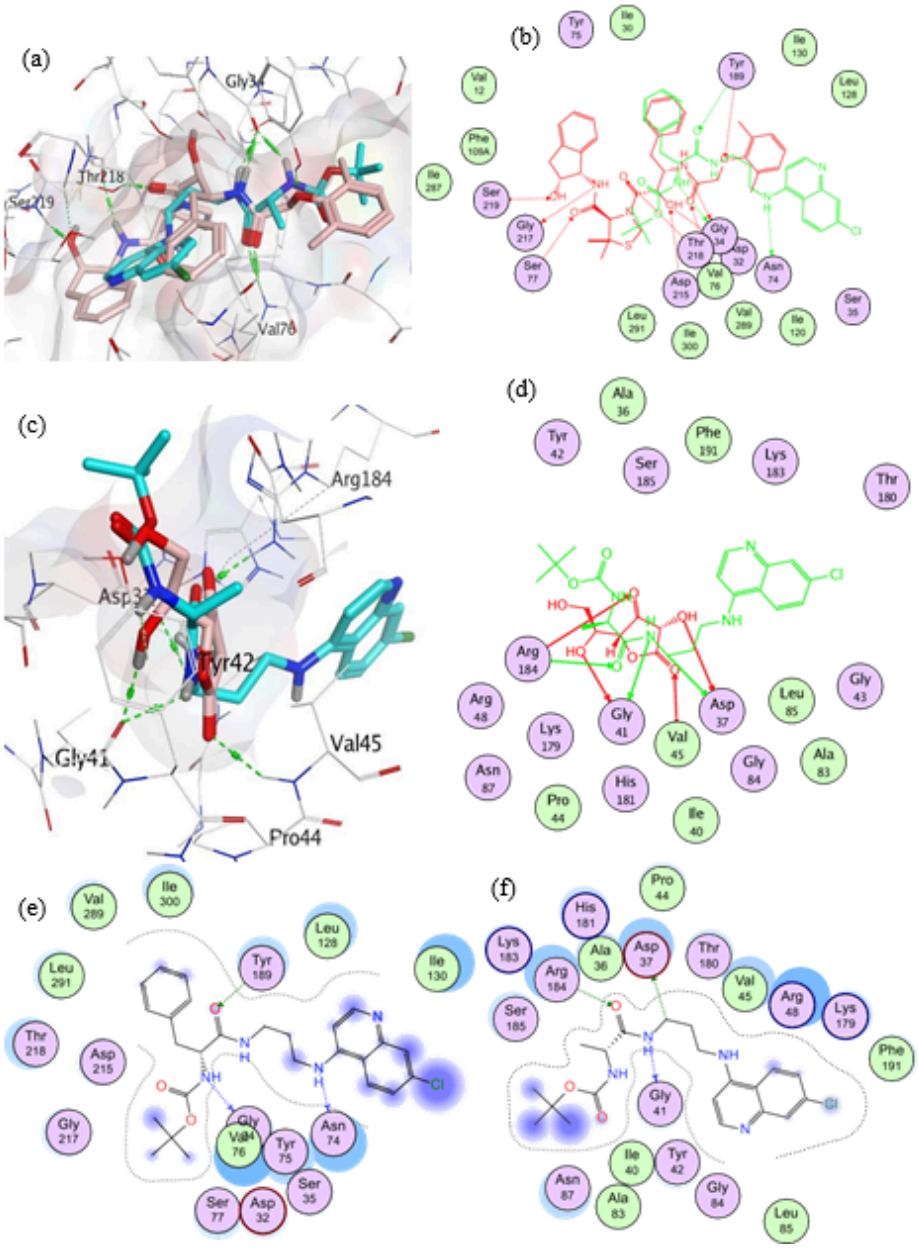

Figure 5

(a) 1b and native ligand in the active binding site of 3QS1 (b) 2D representations showing the binding interactions of 1b and the native ligand (c) 1a and ascorbic acid in the active binding site of 2X08 (d) 2D representations showing the binding interactions of 1a and ascorbic acid. 2D representation of the binding interactions of (e) 1b with 3QS1 and (f) 1a with 2X08