

Synthesis of Quinoline Analogs: Search for Antimalarial Agents

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Summary. Novel synthesis routes for the promising antimalarial agents 4(3-hydroxypyrrolidin-1-yl) and 4(3-hydroxypiperidine-1-yl)-2,8-bis(trifluoromethyl)quinoline have been developed.

Keywords. Quinoline analogs; Antimalarial agents.

Background

Mefloquine, was an effective antimalarial agent first introduced in 1971, that acts on the asexual intraerythrocytic phase, one of the developmental stages of malaria causing parasite [1]. More than a decade before, a resistance of *Plasmodium* sp. emerged as a potential threat to malaria therapy and this, together with unavoidable side effects, *e.g.*, CNS (central nervous system) toxicity, have enforced physicians not to prefer it for prescriptions that resulted in a seldom use of this medicine [2]. Discovery of a cinchona alkaloid as an antimalarial agent played a pivotal role in the identification of lead structures that incorporate a quinoline methanol unit. It is perceptible that an emergence of mefloquine was a result of SAR (structure activity relationship) studies based on structural motif, as a pharmacophore, present in the cinchona alkaloid.

Recently, it has been found that mefloquine enantiomers, (8*R*, 9*S*) and (8*S*, 9*R*), differ in their antimalarial potentials. *In vitro* studies revealed that (+)-(8*S*, 9*R*)- has higher activity than (–)-(8*R*, 9*S*)-mefloquine [2].

It is known that the distance (approximately 3 Å) between the secondary alcohol and nonaromatic secondary or tertiary amine functionalities in the quinoline based antimalarial agents is crucial [3]. Based on this concept, we are actively involved in the search of potential leads as antimalarial agents. Our approach is to install all pharmacophoric elements without changing significantly the quinoline framework. Here, we wish to report the strategy involved in the racemic synthesis of structural type **1**.

Results and Discussion

The present work deals with the condensation of substituted 4-haloquinolines **5** with cyclic amines that led to a synthesis of novel quinoline derivatives **1**. The synthesis commences with the *PPA* mediated condensation of substituted aniline with ethyl trifluoroacetate [4] that afforded corresponding 4-hydroxyquinoline derivatives **3** [5]. Halogenation of **3** employing phosphorus oxyhalide or phosphorus pentachloride yielded corresponding halo derivatives **5** [6]. Alternatively, haloquinones have been prepared *via* tosyl derivatives [7].

To avoid the hazardous nature of transformation of **3** to **5** employing phosphorus oxyhalide or phosphorus pentachloride, we opted to activate the phenolic oxygen with a tosyl moiety to afford **4** and substitute the –OTs in it with an appropriate halide nucleophile as presented in Scheme 1.

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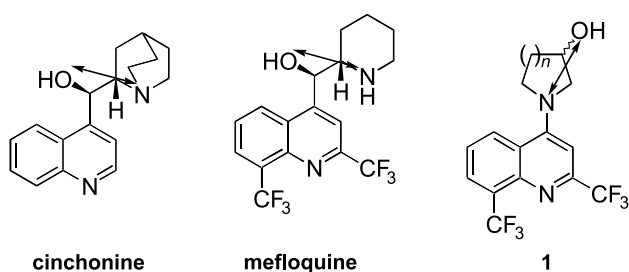
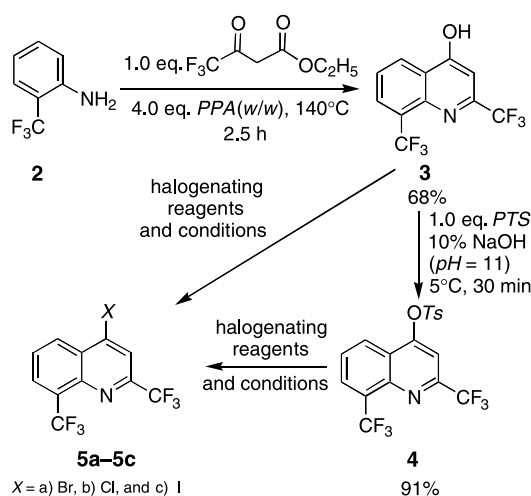


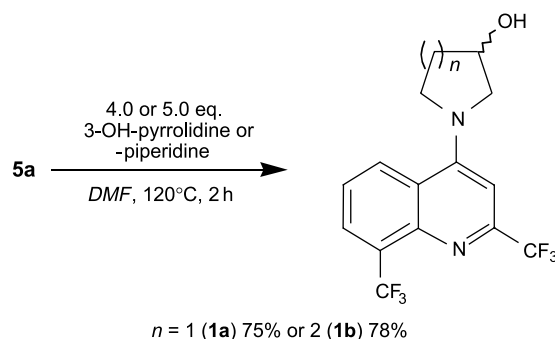
Fig. 1. Similar pharmacophore structural motifs

At first, the tosyl derivative **4** was prepared by refluxing substituted 4-hydroxyquinoline and *p*-toluenesulfonyl chloride (stoichiometric) in chloroform in the presence of triethylamine for 20 h. Despite of excellent yield (90%), the method itself was not efficient because of prolonged refluxing and tedious work-up. To improve the efficiency, acetone, as a solvent, and NaOH, as a base, were used at 0°C



	Reagents (eq.)	Solvent	Time h	Temp. °C	Yield of 5 %
3	POBr ₃ (1.0)	—	3	140	92
3	POCl ₃ (2.0), PCl ₅ (1.0)	—	2	140	63
4	Br ₂ (15), Red 'P' (10)	AcOH	4	25	80
4	CH ₃ COCl (20)	AcOH	6	25	57
4	I ₂ (3), Red 'P' (3)	AcOH	7	140	80

Scheme 1



Scheme 2

to afford the tosylated product **4** in excellent yield (91%).

The 4-bromoquinoline **5a** was reacted separately with hydroxypiperidine and hydroxypyrrolidine, as shown in Scheme 2, to afford the corresponding tertiary amine derivatives **1a** and **1b** in good yields.

Conclusion

In conclusion, we developed an efficient route for the synthesis of quinoline analogs **1a** and **1b**. Syntheses of chiral 4-aminoquinoline derivatives and biological activity testing of these compounds are under progress and the extension of this work will be reported in future.

Experimental

Unless otherwise stated, all non-aqueous reactions and distillations were carried out under an atmosphere of dry nitrogen in dried glassware. When necessary, solvents and reagents were dried *prior to* use. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel aluminum support plates (Merck). Visualization was accomplished by irradiation under a 254 nm UV lamp. ¹H NMR spectra were recorded on a Varian 400 MHz [1]. Chemical shifts are reported in ppm from TMS (0 ppm) or with the solvent resonance as the internal standard (CDCl₃ 7.26 ppm, DMSO-d₆ 2.49 ppm, acetone-d₆ 2.04 ppm, benzene-d₆ 7.15 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, app = apparent quintet, br = broad, m = multiplet), coupling constants, and number of protons. IR spectra were taken on a Perkin-Elmer equipment. Mass spectra were obtained on a low resonance Q-trap machine in electron spray mode. Melting points were obtained on a Polmon apparatus. Compounds **3–5** were prepared according to Refs. [4–7].

1-[2,8-Bis(trifluoromethyl)quinolin-4-yl]pyrrolidin-3-ol (**1a**, C₁₅H₁₂F₆N₂O)

To a solution of 1.0 g (**5a**, 0.0031 mol) in 5 cm³ DMF were added 1.4 g 3-hydroxypyrrolidine (0.016 mol). The resulting

solution was heated to 120°C. After 2 h, the solvent was removed under vacuum, the residue poured into water and extracted with ethyl acetate, washed with water, dried over concentrated, Na₂SO₄ and chromatographed (SiO₂; 30% ethyl acetate/pet ether) to afford 0.89 g **1a** (75%). ¹H NMR (CDCl₃, 200 MHz): δ = 8.31 (d, 2H, *J* = 8.7 Hz), 7.61 (m, 1H), 7.21 (s, 1H), 4.90 (s, 1H), 4.50 (s, 1H), 3.90–4.10 (m, 2H), 3.60–3.80 (m, 2H), 2.80–3.00 (m, 2H) ppm; IR (neat): $\bar{\nu}$ = 3440, 1650, 1280 cm⁻¹; MS (FAB): C₁₅H₁₂F₆N₂O, *m/z* = calcd 350.26, found 349.00 (M–1)

1-[2,8-Bis(trifluoromethyl)quinolin-4-yl]piperidin-3-ol

(**1b**, C₁₆H₁₄F₆N₂O)

To a solution of 1.3 g (**5a**, 0.004 mol) in 8 cm³ DMF were added 1.6 g 3-hydroxypiperidine (0.016 mol). The resulting solution was heated to 120°C. After 2 h, the solvent was removed under vacuum, the residue poured into water and extracted with ethyl acetate, washed with water, dried over sodium sulphate, concentrated, and chromatographed (SiO₂; 30% ethyl acetate/pet ether) to afford **1b** (1.15 g) in 78% yield. ¹H NMR (CDCl₃, 200 MHz): δ = 8.31 (d, 2H, *J* = 8.7 Hz), 7.61 (m, 1H), 7.21 (s, 1H), 2.04–2.06 (m, 1H), 4.90 (s, 1H), 3.43–3.1 (m, 4H), 2.22–1.63 (m, 4H) ppm; IR:

$\bar{\nu}$ = 3400, 1600, 1200 cm⁻¹; MS (FAB): C₁₆H₁₄F₆N₂O, *m/z* = calcd 364.29, found 365.00 (M + 1).

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