Structure Modification of Quinine on C-9 hydroxyl group via Esterification Reaction

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ABSTRACT

Concept the role played by modified quinine in the asymmetric hydroxyl group inspired studies of modified quinine as chiral organic that lead to drug discovery development. A simple and efficient method for C-9 alkylation and arylation of quinine derivatives was reported. Series quinine derivatives were synthesized through the esterification of the hydroxyl group of quinine. The reaction with various alkyl and aryl carbonyl chloride resulted in the series of ester quinine derivatives. The structure of quinine derivatives was characterized by IR, melting point, UV, 1H NMR, 13C NMR, LCMS.

Keywords: synthesis, quinine derivatives, ester

INTRODUCTION

Quinine is an active compound contained in quinine plants and isolated from the bark of a quinine tree. There are around 25 species that generally originate from the Andes mountain valley around Peru and Ecuador. The types that most contain cinchona alkaloids are Cinchona officinalis L., C. calisaya Wedd., C. ledgeriana Moens, and C. pubescens [1], [2]. This plant is widely used as a source of bioactive chemical compounds for the manufacture of drugs, especially quinine compounds which are already known as antimalariai to fight parasites that inhibit human erythrocyte blood. Quinine compounds, which are the main components of secondary metabolites in quinine plants, are still used as malaria drugs which are quite effective. The most abundant compounds of these cinchona alkaloids are quinine, quinidine, cinchonine and cinchonidine which are almost obtained about 16% of the time of the bark of the tree. In addition to the quinine alkaloid compounds, the bark of the quinine tree also contains quinovic acid, quinic acid, phenolic acid, flavonoids, phytosterols [3], [4].

Quinine is used to treat infections caused by Plasmodium falciparum and P. malariae. Quinine acts as a blood schizonticide even though it also has gametocytocidal activity against P. vivax and P. malariae. Because it is a weak base, it is concentrated in the vacuole of P. falciparum food. It is estimated that quinine can act by inhibiting the heme polymerase, thereby allowing the accumulation of cytotoxic substrates. Quinine is also an anti–bacterial, antifungal, cardiotonic, anti-inflammatory, mild antipyretic and analgesic, used generally as a bitter and flavouring agent, also useful in some muscle disorders, especially nocturnal leg cramps and myotonia congenita, because of its direct effect on muscle membranes and sodium channels [5]. The mechanism of action of quinine compounds includes; reduction of oxygen intake and carbohydrate metabolism; impaired DNA and transcription replication through DNA
intercalation; reduction of muscle fiber stimulation through changes in calcium distribution, inhibiting overexpressed P-glycoprotein in tumors that are resistant to multiple drugs and can increase the efficacy of several antineoplastic agents [6]. Quinine is also found to have anti-lipid peroxidase, an antioxidant effect on cancer cells [7] and can inhibit breast, colon and kidney cancer [8], [9], [10], [11], [12], [13]. And also, quinine derivatives are well explored as anti-hyperglycemic activity [14], [15], [16].

![Figure 1. Major Cinchona alkaloids](image)

Cinchona alkaloids (Figure 1), in the last two decades, have reported much interest because of their successful applications in asymmetric synthesis [17], [18], [19], [20]. Cinchona alkaloids have a very important role as chiral bases, phase-transfers catalysts and surface modifiers [21]. The most often used selective synthetic modifications of Cinchona alkaloids were based on the replacement of C-9 hydroxy group by other functionalities, including those with nitrogen, halogen, and chalcogen heteroatoms [22], [23], [24]. Herein we search of an anti-diabetic agent, hereby following the rational approach of drug designing of quinine have been esterification synthesized. To the best of our knowledge, there is only a single, report on the effective building of the new C-C bond by the replacement of the C-9 hydroxyl group. In this paper, we report an expected stereochemical course of the efficient synthesis of a series 9-alkyl and 9-aryl derivatives of quinine. The reaction of the hydroxyl group at C-9 was transformed to the corresponding alkyl carbonyl chloride derivatives and aryl carbonyl chloride derivatives.

**EXPERIMENT**

**Chemicals and instrumentation**

All solvents were dried and distilled according to standard procedure Melting points was determined on a Reichert Thermovar apparatus. The $^1$H- and $^{13}$C-NMR was recorded on JEOL NMR ECZ500R. A 500 MHz for $^1$H-NMR frequency and 125 MHz for $^{13}$C-NMR frequency. Sample was dissolved in deuterated chloroform (CDCl$_3$). Chemical shifts (δ) was reported in parts per million (ppm) and relative to tetramethylsilane (δ 0.00) or CHCl$_3$ residue (δ 7.26) for
Synthesis of ester quinine

Quinine compound (3.244 gr, 10 mmol) was added reagent carbonyl chloride (15 mmol) and then added pyridine (10 mL, 0.12 mol), the reaction mixture was stirred in an oil bath at 150 °C using the stirrer until the product was obtained. Reaction results were monitored using TLC. At the end of the reaction, the resulting mixture was diluted with ethyl acetate/water. The filtrate was washed with water (3 × 100 mL) and dried with Na₂SO₄. The product was purified by column chromatography with the use of ethyl acetate-hexane (2:1). The resulting product was dried and evaporated.

Ester quinine acetate

Yield: (15 mmol, 65 %). Mp : 145-148 °C. ESI-QToF MS m/z 367.19 [M+H]+. FTIR: ν_{max}(cm⁻¹), 3346 (NH), 2924(C-H), 1734(-CO), 1591(-C=C-), 1234(-R-NR'-R'). ¹H-NMR (500 MHz, CDCl₃) δ 1.251 (s, 3H), 1.57 (m, 2H), 1.671 (m, 1H), 1.873 (m, 7H), 2.133 (s, 3H), 2.273 (m, 1H), 2.637 (m, 2H), 3.065 (m, 2H), 3.357 (m, 1H), 3.965 (d, 3H, J=12 Hz), 4.989 (dt, 1H, J=4.5 Hz), 5.010 (d, 1H, J=6 Hz), 5.799 (m, 1H), 6.519 (d, 1H, J=7 Hz), 7.260 (d, 1H, J=4.5 Hz), 7.340 (d, 1H, J=2.5 Hz), 7.349 (d, 1H, J=4.5 Hz), 7.441 (d, 1H, J=4.5 Hz), 8.008 (d, 1H, J=9 Hz), 8.727 (d, 1H, J=4.5 Hz), 13C-NMR (125 MHz, CDCl₃) δ 21.3, 24.2, 27.7, 29.9, 39.7, 42.6, 55.9, 56.6, 59.1, 73.7, 101.5, 114.9, 118.9, 122.1, 127.1, 131.9, 141.6, 143.6, 144.9, 147.5, 158.2, 170.2.

Ester quinine propionate

Yield: (15 mmol, 68 %). Mp : 145-148 °C. ESI-QTOF MS m/z 381.21 [M+H]+. FTIR: ν_{max}(cm⁻¹), 3263 (NH), 2941(C-H), 1737(-CO), 1575(-C=C-), 1236(-R-NR'-R'). ¹H-NMR (500 MHz, CDCl₃) δ 0.997 (dt, 1H, J=6.5 Hz), 1.087 (dt, 3H, J=2 Hz), 1.366 (t, 1H, J=J=10 Hz), 1.495 (t, 3H, J=2 Hz), 1.665 (t, 1H, J=12.5 Hz), 1.811 (m, 7H), 2.106(m, 1H), 2.220 (d, 2H, J=15 Hz), 2.347 (m, 2H), 2.535 (m, 2H), 2.663 (d, 3H, J=4.5 Hz), 2.971 (m, 3H), 3.077 (m, 3H), 3.305 (d, 1H, J=7 Hz), 3.670 (d, 1H, J=13.5 Hz), 3.723 (m, 6H), 3.908 (t, 3H, J=4 Hz), 4.852 (dd, 2H, J=10 Hz), 4.950 (m, 3H), 5.607 (m, 1H), 5.703 (s, 1H), 5.763 (m, 1H), 6.443 (d, 1H, J=7 Hz), 7.097 (d, 1H, J=2.5Hz), 7.168 (m, 1H), 7.287 (dt, 1H, J=4.5 Hz), 7.314 (dt, 1H, J=3 Hz), 7.403 (s, 1H), 7.488 (d, 1H, J=3 Hz), 7.833 (d, 1H, J=5.5 Hz), 7.941 (d, 1H, J=4 Hz), 8.531 (t, 1H, J=7.5 Hz), 8.622 (t, 1H, J=6 Hz). ¹³C-NMR (125 MHz, CDCl₃) δ 9.1, 10.5, 20.6, 24.3, 26.8, 27.6, 27.7, 27.8, 27.8, 30.2, 39.3, 39.7, 42.5, 43.1, 55.7, 55.7, 56.2, 56.6, 59.2, 59.9, 70.1, 73.6, 101.0, 101.5, 114.6, 115.0, 118.7, 118.9, 121.6, 121.9, 126.3, 127.1, 131.4, 131.7, 140.8, 141.7, 143.9, 144.0, 144.7, 147.4, 147.6, 157.8, 158.0, 173.5, 182.2.

Ester quinine hexanoate

Yield: (15 mmol, 72 %). Mp : 145-148 °C. ESI-QToF MS m/z 423.26 [M+H]+. FTIR: ν_{max}(cm⁻¹), 3365 (NH), 2941(C-H), 1737(-CO), 1624(-C=C-), 1234(-R-NR'-R'). ¹H-NMR and δ 77.0 for ¹³C NMR as an internal standard, and coupling constants are reported in Hertz. ESI-QToF MS Mass Spectra were recorded on Waters Xevo® G2-XS QToF. IR spectra were obtained on Bruker Tensor II. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates (Art5715 Kiesel gel 60F₂₅₄ 0.25 mm) and preparative TLC was performed using Merck silica gel plates (Art5744 Kiesel gel 60F₂₅₄ 0.5 mm). Silica gel column chromatography was carried out on Daisogel IR-60. Quinine obtained from the isolation of Chincona ledgeriana Moens was chosen as the starting material, which was characterized by GCMS, LCMS, ESI-QToF MS, ¹H NMR, ¹³C NMR, and FTIR.
NMR (500 MHz, CDCl₃) δ 0.846 (t, 3H, J= 6.5 Hz), 1.270 (m, 5H), 1.605 (m, 4H), 1.736 (m, 1H), 1.842 (m, 1H), 1.866 (s, 1H), 2.301 (s, 1H), 2.375 (dt, 2H, =J= 2Hz), 2.637 (d, 1H, =J= 2 Hz), 2.693 (dt, 1H, =J= 2 Hz), 3.074 (dt, 1H, =J= 3.5Hz), 3.126 (m, 1H), 3.347 (q, 1H), 3.957 (s, 3H), 4.982 (t, 2H, =J= 3.5 Hz), 5.023 (s, 1H), 5.804 (p, 1H), 6.532 (d, 1H, =J= 6 Hz), 7.332 (d, 1H, =J= 4.5 Hz), 7.357 (dd, 1H, =J= 4.5 Hz), 7.447 (d, 1H, =J= 4.5 Hz), 7.999 (d, 1H, =J= 9 Hz), 8.713 (d, 1H, =J= 4.5 Hz), 13C-NMR (125 MHz, CDCl₃) δ 14.0, 22.4, 24.1, 24.7, 27.7, 31.4, 34.6, 39.6, 42.5, 55.9, 56.5, 59.1, 73.4, 101.5, 114.9, 118.9, 122.1, 127.1, 131.8, 141.5, 143.7, 147.5, 158.2, 172.9.

Ester quinine heptanoate

Yield: (15 mmol, 70 %). Mp : 145-148 °C. ESI-QToF MS m/z 437.27 [M+H]⁺.
FTIR: v_{max}(cm⁻¹), 3365 (NH), 2941(C-H), 1737(-CO), 1624(-C=C-), (1234(-R-NR-R')). ¹H-NMR (500 MHz, CDCl₃) δ 0.856 (t, 3H, =J= 6.5 Hz), 1.237 (m, 6H), 1.510 (m, 1H), 1.549 (m, 1H), 1.621 (m, 2H), 1.726 (m, 1H), 1.876 (m, 2H), 2.28 (s, 1H), 2.368 (dt, 2H, =J= 2 Hz), 2.611 (dd, 1H, =J= 2 Hz), 2.667 (dd, 1H, =J= 4 Hz), 3.069 (d, 1H, =J= 10.5Hz), 3.106 (m, 1H), 3.355 (q, 1H), 4.989 (d, 1H, =J= 3 Hz), 5.027 (d, 1H, =J= 2 Hz), 5.825 (p, 1H), 6.496 (d, 1H, =J= 7 Hz), 7.332 (d, 1H, =J= 4.5 Hz), 7.356 (dd, 1H, =J= 3Hz), 7.442 (d, 1H, =J= 2.5Hz), 7.998 (d, 1H, =J= 9 Hz), 8.719 (d, 1H, =J= 4.5 Hz), 13C-NMR (125 MHz, CDCl₃) δ 14.2, 22.6, 25.0, 27.7, 28.9, 31.5, 34.6, 39.8, 55.8, 56.7, 59.2, 73.6, 101.6, 114.7, 119.1, 122.0, 127.2, 131.9, 141.8, 143.9, 147.5, 158.1, 173.0.

Ester quinine benzoate

Yield: (15 mmol, 65 %). Mp : 145-148 °C. ESI-QToF MS m/z 429.44 [M+H]⁺.
FTIR: v_{max}(cm⁻¹), 3369 (NH), 1662(C=O). ¹H-NMR (500 MHz, CDCl₃) δ 1.637 (m, 1H, =J= 6.5 Hz), 1.858 (m, 3H), 1.934 (m, 1H), 1.989 (m, 1H), 2.364 (m, 1H), 2.711 (dd, 1H, =J= 2 Hz), 2.748 (dd, 1H, =J= 4 Hz), 3.168 (t, 1H, =J= 4 Hz), 3.27 (m, 1H), 3.488 (q, 1H), 3.981 (s, 3H), 4.031 (s, 1H), 4.993 (d, 1H, =J= 1.5 Hz), 5.009 (d, 1H, =J= 1.5 Hz), 5.804 (d, 1H, =J= 7 Hz), 6.857 (d, 1H, =J= 5.5 Hz), 7.396 (d, 1H, =J= 4.5 Hz), 7.405 (t, 1H, =J= 5 Hz), 7.472 (t, 2H, =J= 8 Hz), 7.504 (t, 1H, =J= 8 Hz), 7.543 (dd, 1H, =J= 3 Hz), 8.018 (s, 1H), 8.114 (d, 2H, =J= 5 Hz), 8.703 (d, 1H, =J= 4.5 Hz). ¹³C-NMR (125 MHz, CDCl₃) δ 21.7, 22.1, 23.6, 27.0, 27.4, 27.6, 27.7, 39.5, 40.6, 42.6, 55.9, 56.4, 58.1, 59.2, 67.3, 69.5, 72.7, 74.1, 101.4, 101.8, 110.5, 111.7, 118.5, 122.4, 128.9, 129.8, 131.9, 137.4, 141.3, 143.5, 144.8, 147.4, 158.4, 165.5, 171.2, 175.4.

Ester quinine 2-chloro-benzoate

Yield: (15 mmol, 55 %). Mp : 145-148 °C. ESI-QToF MS m/z 463.17 [M+H]⁺.
FTIR: v_{max}(cm⁻¹), 3068 (aromatic), 2935(-CH₃), 1722(-CO), 1624(-RC=CR-), 1465(=NH). ¹H-NMR (500 MHz, CDCl₃) δ 1.250 (s, 1H), 1.788 (m, 2H), 2.340 (m, 1H), 2.722 (m, 2H), 3.122 (t, 1H, =J= 3 Hz), 3.242 (m, 1H), 3.500(m, 1H), 3.955 (s, 3H), 5.011 (m, 1H), 5.045 (t, 1H, =J= 2 Hz), 5.822(m, 1H), 6.833 (d, 1H, =J= 5.5 Hz), 7.355 (m, 1H), 7.372 (m, 1H), 7.457 (m, 2H), 7.487 (m, 3H), 7.496 (d, 1H, =J= 4.5 Hz), 7.850 (dd, 1H, =J= 4.5 Hz), 8.020 (d, 1H, =J= 9.5 Hz), 8.746 (d, 1H, =J= 5 Hz). ¹³C-NMR (125 MHz, CDCl₃) δ 27.9, 41.9, 55.9, 56.5, 59.2, 101.3, 122.4, 127.0, 131.6, 131.9, 133.3, 133.9, 147.3, 158.2, 165.5, 171.2, 175.4.
RESULT AND DISCUSSION

Several studies have reported that cinchona alkaloids were superior, of both catalytic and selectivity activity. Few studies were reported modified cinchona alkaloid derived from a modification of the C-9 hydroxyl group [25]. Quinine is a compound which has bifunctional catalyst properties. Bifunctional quinine by utilizing the presence of tertiary amine groups and hydroxyl groups. Each of these groups is to activate and direct nucleophiles and electrophiles. In the presence of this catalyst's functional catalysis, its asymmetric catalysis properties can be optimized. Due to the basic/nucleophilic catalysis properties of quinine, we use it to modify the structure of quinine compounds for the development of the quinine bioactivity spectrum. In this study, we report the efficient synthesis of a series 9-alkyl and 9-aryl of ester derivative quinine. The reaction of the hydroxyl group at C-9 was transformed to the corresponding alkyl carbonyl chloride derivatives and aryl carbonyl chloride derivatives. The hydroxyl group of quinine reaction with alkyl carbonyl chloride and aryl carbonyl chloride.

Table 1. Reaction quinine with alkyl/aryl carbonyl chloride

| Entry | Compound | R      | MW   | Melting point (°C) | Yield (%) |
|-------|----------|--------|------|-------------------|-----------|
| 1     | Quinine  |        | 324.18 | 324               | -         |
| 2     | Ester quinine acetate | CH3-     | 366.19 | 328               | 65        |
| 3     | Ester quinine propionate | C2H5-     | 380.21 | 339               | 68        |
| 4     | Ester quinine hexanoate | C5H11-    | 422.26 | 373               | 72        |
| 5     | Ester quinine heptanoate | C6H13-    | 436.27 | 384               | 70        |
| 6     | Ester quinine benzoate | C6H5-     | 428.23 | 410               | 65        |
| 7     | Ester quinine 2-chloro benzoate | ClC6H5- | 462.17 | 453               | 55        |
Quinine was reacted with acetyl chloride reagent in base condition. The product was isolated and purified by chromatography in 55-72% yield (Table 1). The structure of ester quinine acetate was elucidated by H-NMR, C-NMR, FTIR, UV and LCMS. The stereochemistry quinine derivatives at position 9 was 9S-quinine ester acetate (2). The same procedure was applied for all quinine derivatives. Quinine was reacted with alkyl and aryl carbonyl chloride (propionyl chloride, hexanoyl chloride, heptanoyl chloride, benzoyl chloride and 2-chloro benzoyl chloride) obtained ester of quinine. All quinine-derived esters are predicted to produce the same stereochemical products as quinine 9S-esters. Its relative configuration was confirmed by 2D NMR experiment (NOESY) (Figure 3). H9 attached in carbon-beta of the ester, has position in the same side to H6, but has no signal interaction to H8. It reveals that H9 is the different side to H8 [26-27]. And also, interaction of H9 to H5' from aromatic ring as indication the twisted bicyclic ring of quinine (Figure 4).

Figure 3. Selected NOE correlation for 9S-ester quinine heptanoate (5)

Figure 4. 3D Structure of 9S-ester quinine heptanoate (5)
CONCLUSION
Our extensive studies of modified quinine have led to the development of a wide variety of new spectrum bioactivity of quinine. 9-OH substituted quinine derivatives were alkylated and arylated in good yield. The reaction with alkyl and aryl carbonyl chloride gave prediction a series of 9S-alkyl ester quinine and 9S-aryl ester quinine compounds. This study highlights quinine-derived compounds with potential abilities for a variety of bioactivity besides antimalarial activity and can be further developed from the modification of the structure of quinine, screening of the design of quinine derivatives by molecular docking, and then be tested for bioactivity in vitro.

CONFLICT OF INTEREST
Authors declare that there is no conflict of interests.

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