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(54) **Title**: NEW PREPARATION OF HYDROXYCHLOROQUINE

(57) **Abstract**: The present invention provides a process for the preparation of hydroxychloroquine by the reaction of 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine under high pressure.

Description

NEW PREPARATION OF HYDROXYCHLOROQUINE

Technical Field

[1] The present invention relates to a process for the preparation of hydroxychloroquine which is therapeutically effective as an anti-malarial drug.

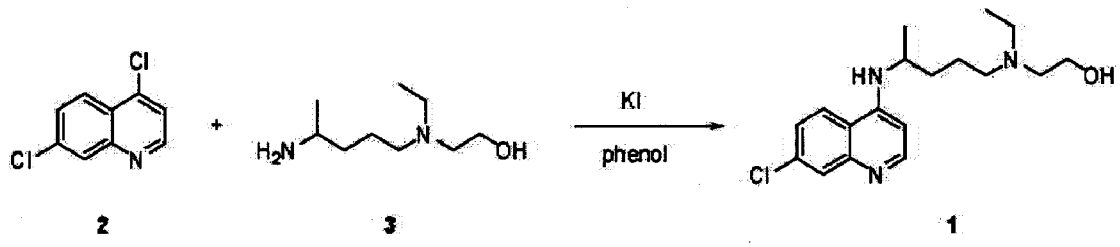
Background Art

[2] Hydroxychloroquine, which is 2-[[4-[7-chloro-4-quinolinyl]amino]pentyl]-ethylamino]ethanol and has a structure of the following formula (1), was first disclosed in US Patent No. 2,546,658. This US patent teaches a process for preparing hydroxychloroquine diphosphate, which involves reacting 4,7-dichloroquinoline of the following formula 2 with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine of the following formula 3 in the presence of potassium iodide (KI) and phenol at a temperature of 125 to 130℃ for 18 hours or more to thereby prepare crude hydroxychloroquine to which diphosphate is then attached to obtain hydroxychloroquine diphosphate with a yield of 35% (see Reaction Scheme 1 below).

[3]

[4] [Reaction Scheme 1]

[5]

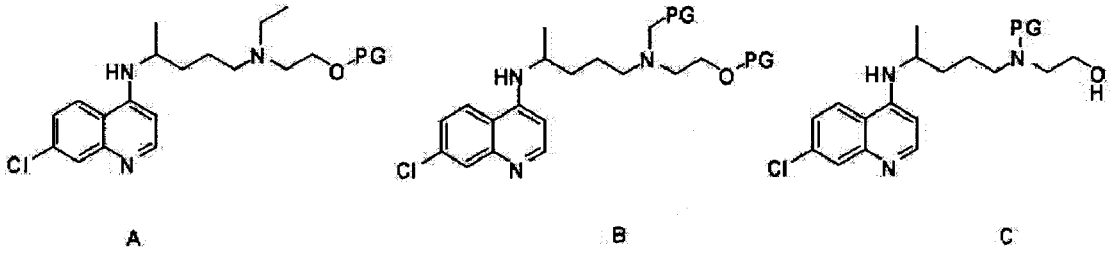


2 3 1

[6] US Patent No. 5,314,894 discloses a process for preparing (S)-(+)-hydroxychloroquine wherein 4,7-dichloroquinoline and (S)-N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine with N,N-diisopropylethylamine (b.p 127℃ were heated at reflux for 48 hours to obtain (S)-(+)-hydroxychloroquine with a yield of 46%.

[7] Further, CA Patent No. 2,561,987 teaches a process for preparing hydroxy-chloroquine, which involves reacting 4,7-dichloroquinoline (2) with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine (3) at a temperature of 120 to 130℃ for 20 to 24 hours, and introducing a protective group, as illustrated below, to the reaction product so as to facilitate the removal of impurities, followed by hydrolysis of the protective group to obtain a desired product hydroxychloroquine.

[8]



[9] In formulae A, B, C, each PG represents a protective group.

[10]

[11] However, with currently known methods of preparing hydroxychloroquine and its acid addition salts, there is a difficulty in elimination of undesirable byproducts upon the preparation of acid addition salts, due to using a toxic solvent such as phenol or a reagent such as N,N-diisopropylethylamine, which has a high boiling point and a structure similar to that of the final product. Particularly, a long reaction time at high temperatures may result in increased production costs and buildup of byproducts, for which a higher-efficiency synthesis method of hydroxychloroquine and disulfate is required in related industrial fields.

[12] To this end, there is a need for the development of a novel method of synthesizing hydroxychloroquine, which is capable of overcoming a variety of problems and disadvantages as discussed above and is capable of providing a desired product with higher purity and yield.

Disclosure of Invention

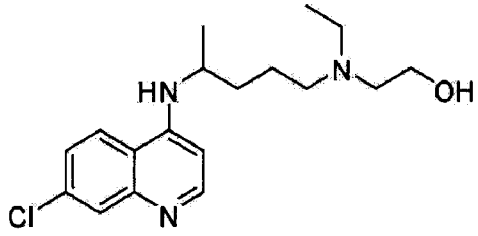
Technical Problem

[13] The present invention is intended to provide a novel method for preparing hydroxychloroquine, which is capable of inhibiting the formation of byproducts and decreasing production costs by significantly decreasing a reaction temperature and a reaction time using a certain pressure, without a catalyst and a reaction solvent.

Technical Solution

[14] The present invention provides a novel method for preparing hydroxychloroquine using a pressure, which comprises reacting 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine under high pressure to obtain hydroxychloroquine of the formula:

[15]



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[16] That is, the method of the present invention provides the preparation of hydroxychloroquine by the reaction of 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine without use of a catalyst and a solvent.

[17] As used herein, the term "high pressure" refers to a more greater pressure than atmospheric pressure(1 atm, about 1 bar), which is preferably in the range of 5 to 30 bars and more preferably 10 to 20 bars.

[18] In the context of the present invention, the high pressure is exerted by an inert gas such as nitrogen (N_2) or argon (Ar) gas or by moisture-free air.

[19] The reaction time is preferably within 10 hours and more preferably 6 hours.

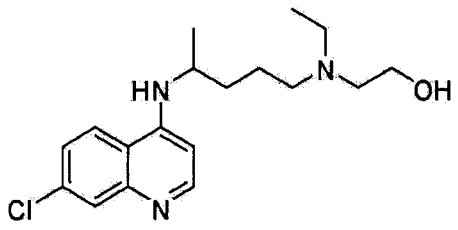
[20] The reaction temperature is preferably in the range of 100 to 120℃, although it may vary.

[21] A reaction molar ratio of 4,7-dichloroquinoline and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine is preferably in the range of 1:1.05 to 1.5 and more preferably 1:1.05 to 1.1, although it may vary.

[22] Further, the present invention provides a process for preparing hydroxychloroquine sulfate, comprising:

[23] (a) reacting 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine under high pressure to obtain hydroxychloroquine of the formula:

[24]



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; and

[25] (b) reacting the hydroxychloroquine of Step (a) with sulfuric acid (H_2SO_4) to obtain hydroxychloroquine sulfate.

[26] Here, reaction conditions for Step (a) are as defined above.

[27] The preparation process of hydroxychloroquine according to the present invention will be described in greater detail hereinafter.

[28] The process is carried out as follows. First, 4,7-dichloroquinoline and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine in a molar ratio of 1:1.1 were placed into a high pressure reactor. Internal pressure of the reactor is then adjusted to the range of 5 to 20 bars and preferably 10 to 15 bars by nitrogen pressure. The reactor is stirred at 80℃ for 30 min until 4,7-dichloroquinoline is completely dissolved, followed by further stirring at a temperature of 100 to 120℃ for 4 to 6 hours.

Advantageous Effects

[29] The present invention enables the production of hydroxychloroquine with high purity and high yield while providing various advantages in that the formation of byproducts is inhibited by decreasing a reaction temperature and significantly decreasing a reaction time using a pressure without use of a catalyst and a reaction solvent, and production costs are reduced.

Mode for the Invention

[30] Now, the present invention will be described in more detail with reference to the following Examples. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

[31] Reagents used in following examples are directly available from Dae He Chemical Co., Ltd. (Korea) or otherwise is purchased from Aldrich. All solvents are commercially available from Samsung Fine Chemical Co., Ltd. (Korea).

[32]

[33] **Example 1: Preparation of hydroxychloroquine using pressure of 20 bars**

[34] 10 kg of 4,7-dichloroquinoline and 11.4 kg (1.0 eq) of N'-ethyl-N'-β -hydroxyethyl-1,4-pentadiamine were introduced into a high pressure reactor which was then filled with nitrogen gas to a pressure of 20 bars and stirred at 80℃ for 30 min, followed by further stirring at 100 to 110℃ for 4 hours. The reactor was cooled to a temperature of about 70 to 80℃. And then 30 kg of a 3N HCl aqueous solution and 20 kg of chloroform were added thereto, and the mixture was cooled to room temperature, stirred for 1 hour, and allowed to stand such that a desired product was transferred to the aqueous layer while the remaining byproducts were transferred to the chloroform layer(This procedure was repeated three times). The aqueous layer containing a desired compound was collected. The thus-collected aqueous layer was extracted again with 40 kg of a 2N NaOH aqueous solution and chloroform to remove the aqueous layer, and 5 kg of activated carbon and 5 kg of alumina was added thereto, followed by stirring at 40℃ for 6 hours and filtration. The filtrate was concentrated under reduced pressure and 60 kg of ethylene dichloride (EDC) was added thereto to result in crystallization. The resulting residue was were filtered and dried under vacuum at 40℃ to afford 14 kg

(yield: 78.2%) of the title compound.

[35]

[36] ^{1}H NMR (500 MHz): δ($CDCl_3$) 7.47(d), 7.92(d), 7.72(d), 7.33(dd), 6.38(d), 5.09(d), 3.50-3.80(m), 2.40-2.70(m), 1.50-1.80(m), 1.30(d), 1.00(t)

[37]

[38] **Example 2: Preparation of hydroxychloroquine (formula 1) using pressure of 10 bars**

[39] 10 kg of 4,7-dichloroquinoline and 11.4 kg (1.0 eq) of N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine were introduced into a high pressure reactor which was then filled with nitrogen gas to a pressure of 10 bars, and stirred at 80℃ for 30 min, followed by further stirring at 100 to 110℃ for 6 hours. The reactor was cooled to a temperature of about 70 to 80℃. And then 30 kg of a 3N HCl aqueous solution and 20 kg of chloroform were added thereto, and the mixture was cooled to room temperature, stirred, and allowed to stand such that a desired product was transferred to the aqueous layer while the remaining byproducts were transferred to the chloroform layer(This procedure was repeated three times). The aqueous layer containing a desired compound was collected. The thus-collected aqueous layer was extracted again with 40 kg of a 2N NaOH aqueous solution and 20 kg of chloroform to remove the aqueous layer, and 5 kg of activated carbon and 5 kg of alumina was added thereto, followed by stirring at 40℃ for 6 hours and filtration. The filtrate was concentrated under reduced pressure and 60 kg of EDC was added thereto to result in crystallization. The resulting residue was filtered and dried under vacuum at 40℃ to afford 14.5 g (yield: 75.5%) of the title compound.

[40]

[41] ^{1}H NMR (500 MHz) values of the obtained compound were identical with those as in Example 1.

[42]

[43] **Example 3: Preparation of hydroxychloroquine sulfate**

[44] 10 kg of hydroxychloroquine prepared in Example 1 was dissolved in 100 kg of ethanol, and the solution was cooled to 10℃. A solution of concentrated sulfuric acid (1.58 kg, 1.0 eq) in 50 kg of ethanol was slowly added thereto with stirring for 12 hours. The reaction solution was filtered to afford 11.0 kg (85.2%) of the title compound as a white material.

[45]

[46] ^{1}H NMR (300 MHz): δ(D_2O) 8.08(d), 7.95(d), 7.53(d), 7.35(dd) 6.64(d), 3.94(d), 3.60-3.70(m), 2.90-3.30(m), 1.50-1.80(m), 1.23(d), 1.09(t)

[47]

[48] **Example 4: Preparation of hydroxychloroquine sulfate**

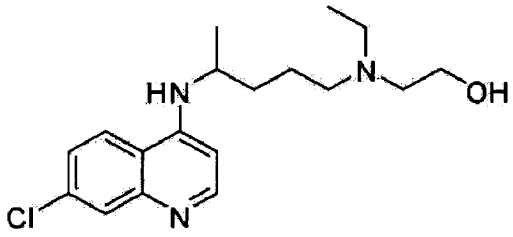
[49] 10 kg of hydroxychloroquine prepared in Example 1 was dissolved in 100 kg of ethyl acetate, and a solution of concentrated sulfuric acid (1.58 kg, 1.0 eq) in 50 kg of ethyl acetate was slowly added thereto with stirring at 30℃. Thereafter, the reaction solution was stirred at 0℃ for 12 hours and filtered to afford 10.0 kg (77.5%) of the title compound as a white material.

[50]

[51] ^{1}H NMR (500 MHz) values of the obtained compound were identical with those as in Example 3.

Claims

[1] A process for preparing hydroxychloroquine, comprising reacting 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine under high pressure to obtain hydroxychloroquine of the formula:



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[2] The process according to claim 1, wherein the reaction is carried out in the absence of catalyst and solvent.

[3] The process according to claim 1, wherein the high pressure is 5 bars or higher.

[4] The process according to claim 3, wherein the high pressure is in the range of 10 to 20 bars.

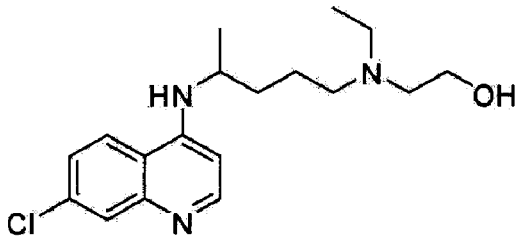
[5] The process according to any one of claims 1 to 4, wherein the high pressure is applied by an inert gas such as nitrogen (N_2) or argon (Ar) gas or by moisture-free air.

[6] The process according to any one of claims 1 to 4, wherein the reaction time is within 6 hours.

[7] The process according to any one of claims 1 to 4, wherein the reaction temperature is in the range of 100 to 120°C.

[8] A process for preparing hydroxychloroquine sulfate, comprising:

(a) reacting 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine under high pressure of nitrogen (N_2) gas to obtain hydroxychloroquine of the formula:



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; and

(b) reacting the hydroxychloroquine of Step (a) with sulfuric acid (H_2SO_4) to obtain hydroxychloroquine sulfate.

[9] The process according to claim 8, wherein the high pressure is 5 bars or higher.

[10] The process according to claim 9, wherein the high pressure is in the range of 10 to 20 bars.

[11] The process according to any one of claims 8 to 10, wherein the high pressure is applied by an inert gas such as nitrogen (N_2) or argon (Ar) gas or by moisture-free air.