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HydroxyChloroQuine (HCQ) Patents : Synthesis & Therapy

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CN108658858 -- Preparing and refining method for hydroxychloroquine and preparation method for sulfate of hydroxychloroquine
CN108689929 -- Preparation method of hydroxychloroquine and sulfate thereof
EP0588430 -- (S)-(+)-Hydroxychloroquine.
CN109280029 -- Preparation method of hydroxychloroquine sulfate
CN103472154 -- Method for analysis of hydroxychloroquine sulfate raw material and preparation by high performance liquid chromatography
KR101115412 -- NEW PREPARATION OF HYDROXYCHLOROQUINE
CN102050781 -- Industrial preparation method of hydroxychloroquine sulfate
CN104230803 -- Preparation method of hydroxychloroquine sulfate
CN107266323 -- Side chain, synthesis method thereof, and method for synthesizing hydroxychloroquine sulfate from side chain
CN107894474 -- Method for simultaneous detection of hydroxychloroquine side chains, raw materials and intermediates by gas chromatography
WO2019165337 -- HIGH-YIELDING CONTINUOUS FLOW SYNTHESIS OF ANTIMALARIAL DRUG HYDROXYCHLOROQUINE
CN105693606 -- Asymmetric synthesis method of optically pure (R)/(S)-hydroxychloroquine
CN103772277 -- Hydroxychloroquine linolenate and synthesis method thereof
CN108658858 -- Preparing and refining method for hydroxychloroquine and preparation method for sulfate of hydroxychloroquine
CN110283121 -- Hydroxychloroquine synthetic method
CN109456266 -- Novel preparation method of hydroxychloroquine sulfate
WO2010027150 -- NEW PREPARATION OF HYDROXYCHLOROQUINE

CN109928925 -- Sublimation purification method of 4,7-dichloroquinoline
WO2010027150 -- NEW PREPARATION OF HYDROXYCHLOROQUINE
CN110627716 -- Preparation method of 4,7-dichloroquinoline
CN103626699 -- Industrial preparation method of 4,7-dichloroquinoline

HCQ Synthesis

CN108658858
Preparing and refining method for hydroxychloroquine and preparation method for

sulfate of hydroxychloroquine

[PDF]

Abstract

The invention discloses a preparing and refining method for hydroxychloroquine and a preparation method for a sulfate of the hydroxychloroquine. The refining method for the hydroxychloroquine comprises the following steps: performing crystallization on a crude product of the hydroxychloroquine in a mixed solvent of a ketone solvent and an ester solvent to obtain a refined product of the hydroxychloroquine, wherein a content of the hydroxychloroquine in the crude product of the hydroxychloroquine is higher than 92%. According to the method disclosed by the invention, purity of the refined product of the hydroxychloroquine prepared by the method can reach 99.9%, a maximum content of a single impurity is controlled within 0.06%, and a total content of other impurities is lower than 0.04%; andpurity of the hydroxychloroquine sulfate prepared from the hydroxychloroquine can reach 99.8%, and a maximum content of a single impurity is controlled within 0.06%.

[0001] Technical field

[0002] The invention relates to a method for preparing and refining hydroxychloroquine and a preparation method thereof.

[0003] Background technique

[0004] Hydroxychloroquine Sulfate, its chemical name is 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol sulfate, CAS No. 747-36- 40. Hydroxychloroquine sulfate was successfully developed by Winthrop and first listed in the United States in 1956. It has been listed in France, Denmark, Japan, Germany, Finland and other countries and regions. On May 29, 1998, the US FDA approved hydroxychloroquine sulfate tablets for the treatment of lupus erythematosus and rheumatoid arthritis.

[0005] US 2,546,658 discloses a process for the synthesis of hydroxychloroquine sulfate, the process of which is as follows:

[0006]

[0007] 4,7-Dichloroquinoline is reacted with 5-(N-ethyl-N-2-hydroxyethylenediylamino)-2-pentylamine (hereinafter referred to as hydroxychloroquine side chain compound) to give hydroxychloroquine, which is then sulfated to form a salt. The patent was reported in 1951, the process is older, the use of equivalent phenol as a solvent, increasing the difficulty of post-processing. Phenol is toxic and corrosive. Its concentrated solution is strongly corrosive to the skin. After treatment, it is converted into sodium phenol wastewater. The phenol-containing wastewater is a kind of hazardous and difficult to treat in industrial wastewater. It is the key control in China. One of the wastewaters has a large environmental pollution, which causes pressure on the treatment of the three wastes; the melting point of phenol is 42 ° C, which is solid at normal temperature. To be successfully fed, it must be heated and dissolved into liquid to be charged, and the operation is very cumbersome. The method is complicated and unsuitable for industrialization, and the yield of the crude hydroxychloroquine obtained is less than 20%.

[0008] CA2561987 discloses a process for preparing hydroxychloroquine. Since the reaction

is maintained at 120-130 ° C for a reaction time of 20-24 h, the impurity content in the crude product is high and the purification process is very complicated. In particular, in the post-treatment, in order to remove the deethylhydroxy chloroquine impurity (7-chloro-4-(4-N-hydroxyethyl-1-methyl-tertiary amino group) as shown in Formula I, a complicated post-treatment process is carried out: An amide group forming agent (for example, an acid anhydride) is reacted with an impurity of the formula I to form a compound of the formula II; and an appropriate amount of a base is added to hydrolyze a compound of the formula III; and under the same conditions of salt formation using hydroxychloroquine, the compound III cannot The salt is formed to remove impurities. In this method, the purification process of hydroxychloroquine and its sulfate is very complicated, the reaction time of the whole route is particularly long, and a large amount of waste water is generated, and complicated post-treatment is performed in order to remove impurities in the post-treatment. The process is costly and is not conducive to industrial production.

[0009] W02010027150 also discloses a method for synthesizing hydroxychloroquine sulfate, which comprises reacting two raw materials, after being pressurized with nitrogen or argon to a pressure of 5-20 bar, stirring at 80 ° C for 30 min, and heating to 100-120 ° C for reaction 4-6h. After the reaction is completed, the hydroxychloroquine is acidified by adding dilute hydrochloric acid and chloroform. At this time, the hydroxychloroquine hydrochloride is dissolved in the aqueous phase, the aqueous phase is collected, alkalized with sodium hydroxide, hydroxychloroquine is extracted with chloroform, and the chloroform layer is concentrated and then dichlorocide is used. The hydroxychloroquine product is obtained after recrystallization of ethane. Hydroxychloroquine is added to sulfuric acid under ethanol as a solvent to obtain hydroxychloroquine sulfate.

[0010] The method still has the following disadvantages: 1. The condensation reaction is promoted by pressurizing in the autoclave, but due to the pressure range of 5-20 bar, there is a great safety hazard in industrial application; The post-treatment of the reaction is to obtain the hydroxychloroquine product by recrystallization after acidification and alkalization, which is equivalent to the use of two refinings, and the product yield is greatly lost. At the same time, the extraction and recrystallization are selected from chloroform and dichloroethane, which are all toxic. Large reagents should be avoided in the production of APIs.

[0011] CN102050781 discloses an industrial production method of hydroxychloroquine sulfate: after heating the reaction liquid to reflux temperature, then gradually raising the temperature for 7-12 hours to 120-125 ° C, distilling off the solvent, and then maintaining the temperature at 120-125 ° C. 13-18 hours. The method prolongs the temperature rise time of the solvent by gradually increasing the temperature during the reaction, and prolongs the temperature rise reaction time below 120 ° C, and the high temperature reaction time is slightly reduced. However, the overall reaction time of the method is still long, the impurities are still more, and the largest single impurity cannot be effectively and stably controlled below 0.1%, and the yield is low. The use of a large amount of organic solvent in the production process for extraction and crystallization, on the one hand increases the cost of the product, on the other hand is not conducive to recycling and environmental protection.

[0012] The method in CN103724261 directly raises the temperature of the two raw materials under gas protection (13-24 hours), has a long reaction time, and the reaction is intense, and generates a large amount of impurities, which is acidified after the post-treatment, and then a large amount of alkali is alkalized, and then The organic solvent is added, so that the organic layer contains a large amount of alkali and inorganic salts, and the hydroxychloroquine which

is crystallized after cooling contains a large amount of inorganic salts and impurities, so that the purity of the hydroxychloroquine HPLC is only 96%, so that the salt is directly obtained by one time. The quality of hydroxychloroquine sulfate is often unqualified.

[0013] In general, the current method for synthesizing hydroxychloroquine sulfate uses a highly toxic catalyst and solvent, which is unfriendly to the environment and increases the production cost. In addition, the production process is cumbersome, the reaction selectivity is poor, the reaction period is long, and special needs are required. The pressure-resistant equipment, the post-reaction treatment is cumbersome and difficult to operate, the production cost is high, and the product impurity content is high. Therefore, it is necessary to further improve the method for preparing hydroxychloroquine sulfate in order to obtain a more efficient, simpler, more selective, environmentally friendly and lower cost method for preparing high-purity hydroxychloroquine sulfate.

[0014] Summary of the invention

[0015] The technical problem to be solved by the present invention is to overcome the defects of the conventional hydroxychloroquine refining method, such as low purity and unstable impurity control, and provide a refining method for effectively controlling the impurity content, greatly improving the purity, and being environmentally friendly.

[0016] The present invention provides a method for purifying hydroxychloroquine, which comprises the steps of: crystallizing a crude hydroxychloroquine in a mixed solvent of a ketone solvent and an ester solvent to obtain a hydroxychloroquine product; the hydroxychloroquine The hydroxychloroquine content in the crude product was >92%.

[0017] The content is calculated by liquid chromatography (HPLC) and calculated by area normalization.

[0018] The hydroxychloroquine boutique preferably has a purity of >99.9%, a maximum single heteropoly control of 0.06%, and a total impurity content of <0.04%.

[0019] The ketone solvent may be conventional in the art, and particularly preferably a C3 to C9 alkyl ketone in the present invention, more preferably one of acetone, methyl ethyl ketone, methyl isobutyl ketone and 2-pentanone or A variety.

[0020] The ester solvent may be conventional in the art, and particularly preferred in the present invention is an acetate solvent, more preferably methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate and acetic acid. One or more of isobutyl esters.

[0021] The mixed solvent is preferably one or more of methyl ethyl ketone and ethyl acetate, acetone and methyl acetate, 2-pentanone and isopropyl acetate, and methyl isobutyl ketone and butyl acetate.

[0022] The mass ratio of the ketone solvent to the ester solvent may be from 1:0.5 to 1:1.5, preferably from 1:0.75 to 1:1.25, more preferably 1:1.

[0023] The mass ratio of the crude hydroxychloroquine to the mixed solvent may be from 1:2 to 1:10; preferably from 1:2.5 to 1:6, more preferably from 1:2.8 to 1:5.

[0024] The crystal may be a conventional crystal in the art. For example, after the crude hydroxychloroquine is dissolved, it is cooled to make the solution supersaturated, and the product is solid precipitated; in the present invention, 65 to 75 ° C is particularly preferred. After dissolving, it was cooled to 10 ° C for crystallization.

[0025] After crystallization of the hydroxychloroquine, the hydroxychloroquine product is preferably obtained by filtration.

[0026] Preferably, the hydroxychloroquine obtained after filtration is washed with the mixed solvent.

[0027] The method for purifying hydroxychloroquine may further comprise the steps of: (1) 4,7-dichloroquinoline and hydroxychloroquine side chain compound (5-(N-ethyl-N) under inert gas protection 2-hydroxyethylenediylamino)-2-pentylamine), the temperature is raised to 105 to 120 ° C for 5 to 20 minutes, and the temperature is raised to 130 to 140 ° C to obtain the hydroxychloroquine; (2) the step The pH of the hydroxychloroquine described in (1) is adjusted to >12, extracted, and washed with water to neutrality to give the crude hydroxychloroquine.

[0028] In the step (1), the inert gas may be conventional in the art so as not to participate in the reaction, and one or more of helium, argon, nitrogen and carbon dioxide are particularly preferred in the present invention.

[0029] In the step (1), the molar ratio of the 4,7-dichloroquinoline to the hydroxychloroquine side chain compound may be 1:1.2 to 1:2, preferably 1:1.4 to 1:1.6.

[0030] In the step (1), the progress of the reaction can be monitored by a conventional monitoring method in the art (for example, TLC, HPLC or NMR), generally when the compound 4,7-dichloroquinoline disappears or no longer reacts. In the present invention, it is particularly preferred to carry out the reaction at 130 to 140 ° C for 3 to 15 hours, more preferably for 8 to 13 hours.

[0031] In the step (1), after the reaction of the 4,7-dichloroquinoline and the hydroxychloroquine side chain compound is completed, it is preferably cooled to 80 ° C or lower.

[0032] In the step (2), the pH adjustment to >12 can be adjusted conventionally in the art, such as one or more of sodium hydroxide, sodium carbonate and potassium hydroxide; in the present invention, the mass percentage is particularly preferred. The aqueous solution of sodium hydroxide having a concentration of 6 to 10%, more preferably 7% by mass.

[0033] The invention also provides a preparation method of hydroxychloroquine, comprising the following steps: (1) 4,7-dichloroquinoline and hydroxychloroquine side chain compound (5-(N-ethyl-) under the protection of an inert gas N-2-hydroxyethylenediylamino)-2-pentylamine), the temperature is raised to 105-120 ° C for 5 to 20 minutes, the temperature is raised to 130-140 ° C to obtain the hydroxychloroquine; (2) the step (The pH of hydroxychloroquine described in 1) is adjusted to >12, extracted, washed with water to neutrality, and crude hydroxychloroquine is obtained.

[0034] In the step (1), the inert gas may be conventional in the art so as not to participate in

the reaction, and one or more of nitrogen, argon, helium and carbon dioxide are particularly preferable in the present invention.

[0035] In the step (1), the molar ratio of the 4,7-dichloroquinoline to the hydroxychloroquine side chain compound may be 1:1.2 to 1:2, preferably 1:1.4 to 1:1.6.

[0036] In the step (1), in the reaction, the progress of the reaction can be monitored by conventional monitoring methods in the art (for example, TLC, HPLC or NMR), generally disappearing with the compound 4,7-dichloroquinoline. In the present invention, it is particularly preferred to carry out the reaction at 130 to 140 ° C for 3 to 15 hours, and more preferably for 8 to 13 hours.

[0037] In the step (1), after the reaction of the 4,7-dichloroquinoline and the hydroxychloroquine side chain compound is completed, it is preferably cooled to 80 ° C or lower.

[0038] In the step (2), the pH to >12 may be conventionally determined in the art, such as one or more of sodium hydroxide, sodium carbonate and potassium hydroxide; in the present invention, the mass percentage concentration is particularly preferred. It is a 6 to 10% aqueous sodium hydroxide solution, and more preferably has a mass percentage concentration of 7%.

[0039] The present invention also provides a process for preparing hydroxychloroquine sulfate, which comprises the steps of: reacting sulfuric acid with a hydroxychloroquine as described above in a solvent to obtain the hydroxychloroquine sulfate.

[0040] Preferably, the hydroxychloroquine has a purity of >99.9%, a maximum single impurity control of 0.06%, and a total impurity content of <0.04%.

[0041] The solvent may be a solvent conventionally used in such a reaction in the art, for example, an alcohol solvent; particularly preferably one or more of methanol, ethanol, isopropanol, propanol, and ethylene glycol;

[0042] The amount of the solvent used in the field is conventionally used in the field. It is particularly preferred in the present invention that the mass ratio of the hydroxychloroquine to the solvent may be from 0.25 g/mL to 0.1 g/mL, preferably 0.2. ~0.15g/mL.

[0043] The amount of the sulfuric acid used may be conventional in the art, for example, the pH is adjusted to 3.5 to 6. In the present invention, it is particularly preferred that the molar ratio of the sulfuric acid to the hydroxychloroquine is 1:0.9 to 1: 1.

[0044] The method for preparing hydroxychloroquine sulfate preferably comprises the steps of: adding the sulfuric acid to the mixture of the hydroxychloroquine and the solvent at 20 to 35 ° C, at 45 ° The reaction is carried out at 65 ° C to obtain the hydroxychloroquine sulfate.

[0045] More preferably, the method for preparing hydroxychloroquine sulfate comprises the steps of: adding the sulfuric acid to the mixture of the hydroxychloroquine and the solvent at 20 to 35 ° C, at 50 The reaction is carried out at -55 ° C to obtain the hydroxychloroquine sulfate.

[0046] After the reaction of the sulfuric acid with the hydroxychloroquine is completed, it is preferably cooled to 0 ° C to 20 ° C, more preferably 0 ° C to 20 ° C.

[0047] The hydroxychloroquine sulfate has a purity of >99.8% and a maximum single impurity of <0.06%.

[0048] The above preferred conditions can be arbitrarily combined without departing from the ordinary knowledge in the art, that is, preferred embodiments of the present invention.

[0049] The reagents and starting materials used in the present invention are commercially available.

[0050] The positive progress of the invention is as follows: 1) avoiding the use of the toxic catalyst phenol, the reaction is carried out under normal pressure, avoiding the danger of high pressure reaction; 2) directly alkalizing in the post-treatment, easy to operate, reducing the liquid alkali By controlling the pH value, not only the number of water washings is reduced, the amount of wastewater is reduced, and the yield is improved; 3) by using a green mixed solvent crystallization, the impurity content of the product is low, and the purity of the hydroxychloroquine obtained by the purification can be Up to 99.9%, the maximum single impurity control is within 0.06%, and the total impurity content is <0.04%; thus, the purity of hydroxychloroquine sulfate can be easily obtained up to 99.8%, and the maximum single impurity control is within 0.06%, which is stable. Control the impurity content to obtain a high purity product.

[0051] DRAWINGS

[0052] Figure 1 is an HPLC chart of crude hydroxychloroquine in Example 4;

[0053] Figure 2 is a HPLC diagram of the hydroxychloroquine in Example 4;

[0054] Figure 3 is an HPLC chart of hydroxychloroquine sulfate in Example 4.

[0055] Detailed ways

[0056] The invention is further illustrated by the following examples, which are not intended to limit the invention. The experimental methods in the following examples which do not specify the specific conditions are selected according to conventional methods and conditions, or according to the product specifications.

[0057] Example 1

[0058] a. Preparation of hydroxychloroquine

[0059] 100 g of 4,7-dichloroquinoline and 110 g of hydroxychloroquine side chain compound (5-(N-ethyl-N-2-hydroxyethylenediylamino)-2-pentylamine, hereinafter referred to as side chain) were added to the reactor. Into the nitrogen protection, the temperature is raised at 78 ° C to dissolve 4,7-dichloroquinoline, the temperature is raised at 120 ° C for 20 minutes, the temperature is raised at 130 ° C for 8 hours, after the reaction is completed, the temperature is lowered (below 80 ° C), with sodium hydroxide solution (mass concentration was 7%), the pH was adjusted to 12, extracted with dichloromethane, washed with water until neutral, and

dichloromethane was evaporated under reduced pressure to give 154 g of crude chlorochloroquine. The yield was 90.7%, and the HPLC purity was 92.45%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.93%, a maximum single impurity of 0.05%, and a yield of 90.3%.

[0060] b. Preparation of hydroxychloroquine sulfate

[0061] 100 g of hydroxychloroquine was dissolved in 500 g of absolute ethanol, and concentrated sulfuric acid was added dropwise at 20 ° C to adjust the solution to turbidity (pH 3.5 to 5), the temperature was raised at 45 ° C for 10 hours, cooled to 20 ° C for 1 hour, and filtered to obtain sulfuric acid. Hydroxychloroquine, purity 99.93%, maximum single impurity 0.05%, yield 94.5%.

[0062] Example 2: Preparation of hydroxychloroquine sulfate

[0063] a. Preparation of hydroxychloroquine

[0064] 100g of 4,7-dichloroquinoline and 130g side chain were added to the reactor, protected by argon gas, heated at 70 ° C to dissolve 4,7-dichloroquinoline, heated at 115 ° C for 10 minutes, and heated at 137 ° C. After 10 hours, after the reaction is completed, the temperature is lowered (below 80 ° C), adjusted to pH > 12 with sodium hydroxide solution (mass concentration 6%), extracted with dichloromethane, washed with water until neutral, and distilled off dichloromethane to obtain hydroxychloroquine under reduced pressure. The crude product was 157 g, the yield was 92.5%, and the HPLC purity was 93.96%. Add 200g of acetone and 250g of methyl acetate to the whole amount of hydroxychloroquine and heat to dissolve at 65 °C. After 4h, slowly cool down to 10 °C, filter, and filter cake washed with mixed solvent of acetone and methyl acetate to obtain hydroxychloroquine wet product. After drying at 60 ° C for 4 h, hydroxychloroquine dry product was obtained, the purity was 99.94%, the maximum single impurity was 0.04%, and the yield was 89.1%.

[0065] b. Preparation of hydroxychloroquine sulfate

[0066] 100 g of hydroxychloroquine was dissolved in 500 g of absolute ethanol, and concentrated sulfuric acid was added dropwise at 25 ° C until the solution became cloudy. The temperature was raised at 50 ° C for 9 hours, cooled to 20 ° C for 1 h, and filtered to obtain hydroxychloroquine sulfate. The purity was 99.94%. Single impurity 0.04%, yield 94.2%.

[0067] Example 3: Preparation of hydroxychloroquine sulfate

[0068] a. Preparation of hydroxychloroquine

[0069] 100g of 4,7-dichloroquinoline and 130g of side chain were added to the reactor, protected by helium gas, heated at 70 ° C to dissolve 4,7-dichloroquinoline, heated at 115 ° C for 15 minutes, and heated at 135 ° C. After 11 hours, after the reaction is completed, the temperature is lowered (below 80 ° C), adjusted to pH > 12 with sodium hydroxide solution

(mass concentration: 10%), extracted with dichloromethane, washed with water until neutral, and distilled off dichloromethane to obtain hydroxychloroquine under reduced pressure. The crude product was 158 g, the yield was 93.1%, and the HPLC purity was 93.73%. Add 400g of 2-pentanone to 350g of isopropyl acetate to the whole amount of hydroxychloroquine, heat it at 65 °C, slowly cool to 10 °C after 4h, filter, filter cake mixed solvent of 2-pentanone and isopropyl acetate mixed solution After washing, hydroxychloroquine wet product was obtained, and dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product, the purity was 99.93%, the maximum single impurity was 0.04%, and the yield was 89.7%.

[0070] b. Preparation of hydroxychloroquine sulfate

[0071] Dissolve 100g of hydroxychloroquine in 500g of absolute ethanol, add concentrated sulfuric acid to the solution turbid at 30 °C, heat up at 55 ° C for 7 hours, cool to 20 ° C for 1 h, filter to obtain hydroxychloroquine sulfate, purity 99.93%, maximum The single impurity was 0.04%, and the yield was 94.7%.

[0072] Example 4: Preparation of hydroxychloroquine sulfate

[0073] a. Preparation of hydroxychloroquine

[0074] 100g of 4,7-dichloroquinoline and 175g of side chain were added to the reactor, protected by CO2, heated at 68 ° C to dissolve 4,7-dichloroquinoline, heated at 105 ° C for 5 minutes, and heated to 132 ° C. After the reaction is completed, the temperature is lowered (below 80 ° C), the pH is adjusted to 12 with sodium hydroxide solution (mass concentration 7%), extracted with dichloromethane, washed with water until neutral, and dichloromethane is distilled off under reduced pressure to obtain crude hydroxychloroquine. 156 g, the yield was 96.26%, and the HPLC purity was 93.36%. Add 400g of methyl isobutyl ketone to 300g of butyl acetate in the crude amount of hydroxychloroquine, heat it at 65 °C, slowly cool to 10 °C after 4h, filter, filter cake mixed with methyl isobutyl ketone and butyl acetate mixed solvent After washing, hydroxychloroquine wet product was obtained, and dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.92% and a maximum single impurity of 0.05%.

[0075] Table 1. Contents in crude hydroxychloroquine and HPLC (Figures 1 and 2)

[0076]

[0077] Note: 1. The relative retention time is based on the retention time of hydroxychloroquine HPLC; that is, the relative retention time is “1” for hydroxychloroquine, and the other relative retention time is impurity.

[0078] b. Preparation of hydroxychloroquine sulfate

[0079] 100 g of hydroxychloroquine was dissolved in 500 g of absolute ethanol, and concentrated sulfuric acid was added dropwise at 35 ° C until the solution became cloudy. The temperature was raised at 65 ° C for 4 hours, cooled to 20 ° C for 1 h, and filtered to obtain hydroxychloroquine sulfate. The purity was 99.88%. Single miscellaneous <0.06%, yield 93.6%.

[0080] Table 2. Content in % of hydroxychloroquine sulfate HPLC (Figure 3)

[0081] Retention time (min) 5.676 7.013 9.998 10.597 12.223 16.655 Content% 0.0527 0.0040 0.0483 0.0074 0.0034 99.8839

[0082] Comparative Example 1

[0083] 100g side chain, 112g 4.7-dichloroquinoline was added to a three-necked flask, protected by nitrogen, heated to 100 ° C, stirred for 1 h, then heated to 120-130 ° C for 20 h, after the reaction was completed, the temperature was lowered (below 80 ° C), with hydroxide The sodium solution was adjusted to pH > 12, extracted with dichloromethane, washed with water until neutral, and dichloromethane was evaporated under reduced pressure to give 147 g of crude chlorochloroquine. The yield was 86.6%, and the HPLC purity was 90.47%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 20 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.80%, a maximum single impurity of 0.12%, and a yield of 88.2%.

[0084] Comparative Example 2

[0085] 100g of 4,7-dichloroquinoline and 110g of side chain were added to the reactor, protected by nitrogen, heated at 78 ° C to dissolve 4,7-dichloroquinoline, heated at 120 ° C for 20 minutes, and heated to 140 ° C. After the reaction is completed, the reaction solution is cooled to 90 ° C ~ 100 ° C, 5% sodium hydroxide solution is added, alkalized to neutral, extracted with dichloromethane, and added to the combined organic phase, 250 g of drinking water is added. The layering was repeated until the pH of the washing water was 7, and methylene chloride was distilled off under reduced pressure to give 164 g of crude hydroxy chloroquine. The yield was 96.9%, and the HPLC purity was 91.78%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.70%, a maximum single impurity of 0.21%, and a yield of 75.3%.

[0086] Comparative Example 3

[0087] a. Preparation of hydroxychloroquine

[0088] 100g of 4,7-dichloroquinoline and 110g of side chain were added to the reactor, protected by nitrogen, heated at 78 ° C to dissolve 4,7-dichloroquinoline, heated at 120 ° C for 20 minutes, and heated to 140 ° C. After the reaction is completed, the temperature is lowered (below 80 ° C), the pH is adjusted to 12 with sodium hydroxide solution, extracted with dichloromethane, washed with water until neutral, and dichloromethane is evaporated under reduced pressure to give crude chlorochloroquine 146 g, yield: 86.7%. The HPLC purity was 90.49%. Add 400g of isopropyl acetate to the crude hydroxychloroquine, then add 5.0g of activated carbon, reflux at elevated temperature for 1 hour, heat filtration, the filtrate is cooled to 0 ° C, crystallization for 2 h, filtered, and dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product. . The purity was 99.63%, the maximum single impurity was 0.091%, and the yield was 88.1%.

[0089] b. Preparation of hydroxychloroquine sulfate

[0090] 100 g of hydroxychloroquine obtained in the previous step was dissolved in 500 g of absolute ethanol, concentrated sulfuric acid was added dropwise at 25 ° C until the solution became cloudy, the temperature was raised at 50 ° C for 9 hours, cooled to 20 ° C for 1 h, and filtered to obtain hydroxychloroquine sulfate, purity 99.74. %, the largest single impurity 0.17%, the yield was 90.2%.

[0091] Comparative Example 4

[0092] a. Preparation of hydroxychloroquine

[0093] 100g of 4,7-dichloroquinoline and 110g of side chain were added to the reactor, protected by nitrogen, heated at 78 ° C to dissolve 4,7-dichloroquinoline, heated at 120 ° C for 20 minutes, and heated to 140 ° C. After the reaction is completed, the temperature is lowered (below 80 ° C), adjusted to pH > 12 with sodium hydroxide solution, extracted with dichloromethane, washed with water until neutral, and dichloromethane is evaporated under reduced pressure to give crude hydroxychloroquine 149 g, yield 87.8%. The HPLC purity was 90.91%. To the crude hydroxychloroquine, 300 g of ethyl acetate was added, and the mixture was heated to dissolve, and the temperature was lowered to 0 to 10 ° C. After incubation for 2 hours, the mixture was filtered and dried to obtain a hydroxychloroquine dry product. The purity was 99.63%, the maximum single impurity was 0.095%, and the yield was 89.6%.

[0094] b. Preparation of hydroxychloroquine sulfate

[0095] 100g of hydroxychloroquine obtained in the previous step is dissolved in 500g of absolute ethanol, concentrated sulfuric acid is added dropwise at 25 °C until the solution is cloudy, heated at 50 ° C for 9 hours, cooled to 20 ° C for 1 h, and filtered to obtain hydroxychloroquine sulfate, purity 99.79 %, the largest single impurity is 0.18%, and the yield is 89.2%.

[0096] Comparative Example 5

[0097] In a three-necked round bottom flask, 4,7-dichloroquinoline (198 g, 1.0 mol), hydroxychloroquine side chain (182 g, 1.05 mol) and isopropyl acetate 1089 g were added, and sodium ethoxide (13.6 g, 0.2 mol) was slowly added. The temperature is slowly raised to reflux under stirring conditions, and then isopropyl acetate is distilled off, and the temperature is gradually raised to 110 ° C over 9 hours, then heated to 120-122 ° C for 10 hours, and finally heated at 120-122 ° C for 4 hours, until the reaction is complete. Thereafter, the reaction solution was cooled to 90 to 100 ° C, directly added to a 5% sodium hydroxide solution, and alkalized to neutrality. The distilled isopropyl acetate was extracted twice, and the layers were separated. 500 g of drinking water was added to the combined organic phase, washed, layered, and the above operation was repeated until the pH of the washing water was 7. After the washing was completed, the water temperature was controlled to 65 ° C, and isopropyl acetate was distilled off under reduced pressure to obtain crude hydroxychloroquine. The HPLC purity was 91.78%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the

filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.8%, a maximum single impurity of 0.17%, and a yield of 87.6%.

[0098] Comparative Example 6

[0099] 20g side chain, 22.4g 4.7-dichloroquinoline was added to a three-necked flask, protected by nitrogen, heated to 100 ° C, stirred for 1 h, then heated to 120-130 ° C for 20 h, the reaction was completed, slightly cooled (90 ° C ~ 100 ° C) 20 g of water was added to the reaction solution, and 40 g of concentrated hydrochloric acid was added. After stirring, 80 g of liquid alkali was added, and the mixture was stirred for 30 minutes. The aqueous phase was discarded, and the organic solvent was evaporated under reduced pressure to obtain a crude product. HPLC purity was 90.2%. The crude product was added with 300 g of methyl ethyl ketone and 300 g of ethyl acetate, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxy chloroquine wet product, 60 ° C. The dried hydroxychloroquine was dried for 4 h, the purity was 99.80%, the maximum single impurity was 0.13%, and the yield was 88.2%.

[0100] Comparative Example 7

[0101] 100 g of crude hydroxychloroquine (HPLC purity greater than 92%) obtained in Example 1 was placed in a single-mouth bottle, and a mixed solvent of 260 g of ethyl acetate and 40 g of isopropyl alcohol was added thereto, and the mixture was stirred at a temperature, and slowly heated to 80 ° C, refluxing 1 After the hour, the temperature is lowered to 15-20 ° C, the crystallization time is started for 5 hours, the temperature is lowered to 0 to 5 ° C, the crystal is separated by filtration, and the filter cake is washed with ethyl acetate to obtain hydroxychloroquine wet product, which is dried to obtain fine hydroxychloroquine. The HPLC purity was 99.7%, the maximum single impurity was 0.16%, and the yield was 75%.

[0102] Comparative Example 8

[0103] 100 g of crude hydroxychloroquine (HPLC purity greater than 92%) obtained in Example 1 was placed in a single-mouth bottle, and a mixed solvent of 260 g of ethyl acetate and 40 g of isopropyl alcohol was added thereto, and the mixture was stirred and dissolved at a temperature. After completely dissolved, 4.2 g was added. Activated carbon, slowly warmed to 80 ° C, reflux for 1 hour, hot filtered, filter cake washed with 26g of ethyl acetate and 4g of isopropanol mixed solvent, the filtrate was combined, cooled to 15 ~ 20 ° C, began crystallization time 5 hours, cooling to 0 to 5 ° C, after thermal crystallization, filtration, the filter cake was washed with ethyl acetate to obtain hydroxy chloroquine wet product, which was dried to obtain HPLC hydroxychloroquine with a purity of 99.8%, a maximum single impurity of 0.11%, and a yield of 70%.

[0104] Comparison of Example 1 and Comparative Examples 3 and 4

[0105] table 3.

[0106]

[0107]

[0108] Table 4.

[0109]

[0110] Note: 1. The relative retention time is based on the retention time of hydroxychloroquine HPLC; that is, the relative retention time is “1” for hydroxychloroquine, and the other relative retention time is impurity.

[0111] After refining, in Example 1, the content of impurity 1 was controlled to be <0.06%; the content of the remaining impurities was one order of magnitude lower than that of the comparative example, and the total amount of remaining impurities was <0.04%. The main impurity content in the comparative example was 0.085-0.1%, both of which were close to 0.1%. The impurity content could not be stably controlled, and it was easy to be >0.1% in the subsequent storage process.

CN108689929
Preparation method of hydroxychloroquine and sulfate thereof
[PDF]

Abstract
The invention discloses a preparation method of hydroxychloroquine and sulfate thereof. The preparation method of the hydroxychloroquine comprises the following steps of step (1), under the inert gasprotection atmosphere, enabling 4,7-dichloroquine and hydroxychloroquine side chain compounds to react at the temperature of 134 to 144 DEG C until the content of 4,7-dichloroquine is smaller than orequal to 10%, so as to obtain a crude product of the hydroxychloroquine, wherein the content of the hydroxychloroquine in the crude product of the hydroxychloroquine is greater than 92%; step (2), recrystallizing the obtained crude product of the hydroxychloroquine in step (1) in a mixed solvent of alcohol solvent and ester solvent, so as to obtain a refined product of the hydroxychloroquine. Thepurity of the refined product of the hydroxychloroquine can reach 99.9%, the maximum content of single impurity is controlled within 0.06%, and the total content of other impurities is smaller than 0.04%.

[0001] Technical field

[0002] The present invention relates to a process for the preparation of hydroxychloroquine and its sulfate.

[0003] Background technique

[0004] Hydroxychloroquine Sulfate, its chemical name is 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol sulfate, CAS No. 747-36- 40. Hydroxychloroquine sulfate was successfully developed by Winthrop and first listed in the United States in 1956. It has been listed in France, Denmark, Japan, Germany, Finland and other countries and regions. On May 29, 1998, the US FDA approved hydroxychloroquine sulfate tablets for the treatment of lupus erythematosus and rheumatoid arthritis.

[0005] US 2,546,658 discloses a process for the synthesis of hydroxychloroquine sulfate, the process of which is as follows:

[0006]

[0007] 4,7-Dichloroquinoline is reacted with 5-(N-ethyl-N-2-hydroxyethylenediylamino)-2-pentylamine (hereinafter referred to as hydroxychloroquine side chain compound) to give hydroxychloroquine, which is then sulfated to form a salt. The patent was reported in 1951, the process is older, the use of equivalent phenol as a solvent, increasing the difficulty of post-processing. Phenol is toxic and corrosive. Its concentrated solution is strongly corrosive to the skin. After treatment, it is converted into sodium phenol wastewater. The phenol-containing wastewater is a kind of hazardous and difficult to treat in industrial wastewater. It is the key control in China. One of the wastewaters has a large environmental pollution, which causes pressure on the treatment of the three wastes; the melting point of phenol is 42 ° C, which is solid at normal temperature. To be successfully fed, it must be heated and dissolved into liquid to be charged, and the operation is very cumbersome. The method is complicated and unsuitable for industrialization, and the yield of the crude hydroxychloroquine obtained is less than 20%.

[0008] CA2561987 discloses a method for preparing hydroxychloroquine. Since the reaction is maintained at 120-130 ° C for a reaction time of 20-24 h, the impurity content in the crude product is high and the purification process is complicated. In particular, in the post-treatment, in order to remove the deethylhydroxy chloroquine impurity (7-chloro-4-(4-N-hydroxyethyl-1-methyl-tertiary amino group) as shown in Formula I, a complicated post-treatment process is carried out: An amide group forming agent (for example, an acid anhydride) is reacted with an impurity of the formula I to form a compound of the formula II; and an appropriate amount of a base is added to hydrolyze a compound of the formula III; and under the same conditions of salt formation using hydroxychloroquine, the compound III cannot The salt is formed to remove impurities. In this method, the purification process of hydroxychloroquine and its sulfate is very complicated, the reaction time of the whole route is particularly long, and a large amount of waste water is generated, and complicated post-treatment is performed in order to remove impurities in the post-treatment. The process is costly and is not conducive to industrial production.

[0009] W02010027150 also discloses a method for synthesizing hydroxychloroquine sulfate, which comprises reacting two raw materials, after being pressurized with nitrogen or argon to a pressure of 5-20 bar, stirring at 80 ° C for 30 min, and heating to 100-120 ° C for reaction 4-6h. After the reaction is completed, the hydroxychloroquine is acidified by adding dilute hydrochloric acid and chloroform. At this time, the hydroxychloroquine hydrochloride is dissolved in the aqueous phase, the aqueous phase is collected, alkalized with sodium hydroxide, hydroxychloroquine is extracted with chloroform, and the chloroform layer is concentrated and then dichlorocide is used. The hydroxychloroquine product is obtained after recrystallization of ethane. Hydroxychloroquine is added to sulfuric acid under ethanol as a solvent to obtain hydroxychloroquine sulfate.

[0010] The method still has the following disadvantages: 1. The condensation reaction is promoted by pressurizing in the autoclave, but due to the pressure range of 5-20 bar, there is a great safety hazard in industrial application; The post-treatment of the reaction is to obtain the hydroxychloroquine product by recrystallization after acidification and alkalization, which is equivalent to the use of two refinings, and the product yield is greatly lost. At the same time,

the extraction and recrystallization are selected from chloroform and dichloroethane, which are all toxic. Large reagents should be avoided in the production of APIs.

[0011] CN102050781 discloses an industrial production method of hydroxychloroquine sulfate: after heating the reaction liquid to reflux temperature, then gradually raising the temperature for 7-12 hours to 120-125 ° C, distilling off the solvent, and then maintaining the temperature at 120-125 ° C. 13-18 hours. The method prolongs the temperature rise time of the solvent by gradually increasing the temperature during the reaction, and prolongs the temperature rise reaction time below 120 ° C, and the high temperature reaction time is slightly reduced. However, the overall reaction time of the method is still long, the impurities are still more, and the largest single impurity cannot be effectively and stably controlled below 0.1%, and the yield is low. The use of a large amount of organic solvent in the production process for extraction and crystallization, on the one hand increases the cost of the product, on the other hand is not conducive to recycling and environmental protection.

[0012] The method in CN103724261 directly raises the temperature of the two raw materials under gas protection (13-24 hours), has a long reaction time, and the reaction is intense, and generates a large amount of impurities, which is acidified after the post-treatment, and then a large amount of alkali is alkalized, and then The organic solvent is added, so that the organic layer contains a large amount of alkali and inorganic salts, and the hydroxychloroquine which is crystallized after cooling contains a large amount of inorganic salts and impurities, so that the purity of the hydroxychloroquine HPLC is only 96%, so that the salt is directly obtained by one time. The quality of hydroxychloroquine sulfate is often unqualified.

[0013] In general, the current method for synthesizing hydroxychloroquine sulfate has the use of highly toxic catalysts and solvents, which are environmentally unfriendly and increase the production cost. In addition, the production process is cumbersome, the reaction selectivity is poor, the reaction cycle is long, and special resistance is required. The pressure equipment, the post-reaction treatment are cumbersome and difficult to operate, the production cost is high, and the product impurity content is high. Therefore, it is necessary to further improve the method for preparing hydroxychloroquine sulfate in order to obtain a more efficient, simpler, more selective, environmentally friendly and lower cost method for preparing high-purity hydroxychloroquine sulfate.

[0014] Summary of the invention

[0015] The technical problem to be solved by the present invention is the preparation method of the existing hydroxychloroquine, which has the defects of low purity and unstable impurity control, and provides a preparation method of hydroxychloroquine and its sulfate. By adopting the preparation method, the impurity content can be effectively and stably controlled, the purity is greatly improved, and the environment is environmentally friendly.

[0016] The invention provides a preparation method of hydroxychloroquine sulfate, which comprises the steps of: forming a salt reaction of a sulfuric acid aqueous solution with a hydroxychloroquine in a solvent to obtain the hydroxychloroquine sulfate; the aqueous sulfuric acid solution; The mass percentage is 30% to 80% aqueous sulfuric acid; the purity of the hydroxychloroquine is >99.0% by mass.

[0017] Wherein the hydroxychloroquine sulfate is preferably a crystal; the crystal has an X-ray powder diffraction represented by a 2θ angle having characteristic peaks at the following

positions: 16.9°, 17.1°, 17.5°, 19.9°, 21.3°, 23.5°, 23.9° and 26.7°. Preferably, the XRPD pattern of the hydroxychloroquine sulfate form is shown in FIG.

[0018] Wherein the hydroxychloroquine sulfate is preferably characterized by an infrared absorption spectrum measured by KBr tableting, which has characteristic peaks at the following positions: 3424, 3214, 2972, 1613, 1553, 1458, 1366, 1342, 1215 , 1111, 824, 620, and 605 cm-1.

[0019] Wherein the hydroxychloroquine sulfate, preferably differential scanning calorimetry (DSC), has an endothermic peak at 246 °C.

[0020] Among them, in the hydroxychloroquine boutique, preferably, the maximum single heteropoly is controlled within 0.06%, and the total impurity content is <0.04%.

[0021] The aqueous sulfuric acid solution is preferably from 40% to 60% by mass, more preferably 50% by mass.

[0022] Wherein, the solvent is preferably an alcohol solvent (for example, one or more of ethanol, methanol and isopropanol), or an alcohol solvent (for example, one or more of ethanol, methanol and isopropanol). a mixed solvent with an ester solvent such as ethyl acetate.

[0023] In the mixed solvent, the weight of the alcohol solvent and the ester solvent is preferably from 1:0.2 to 1:0.8.

[0024] Wherein, the amount of the solvent is generally such that the hydroxychloroquine is completely dissolved to form a uniform solution. The weight of the hydroxychloroquine and the solvent is preferably from 1:3 to 1:8 (again, for example, from 1:4 to 1:5).

[0025] Wherein, the amount of the sulfuric acid used may be a conventional amount in the art, for example, the pH is adjusted to 3.5 to 6. The molar ratio of the sulfuric acid and the hydroxychloroquine in the present invention is preferably 1:0.9. 1:1.

[0026] The method for preparing hydroxychloroquine sulfate preferably further comprises the steps of: adding the sulfuric acid to the mixture of the hydroxychloroquine and the solvent at 20 to 35 ° C; The reaction is carried out at 30 to 55 ° C to obtain the hydroxychloroquine sulfate. Preferably, after the sulfuric acid is added dropwise, the reaction is carried out at 50 to 55 °C.

[0027] Wherein, after the reaction of the sulfuric acid with the hydroxychloroquine is completed, it is preferably cooled to 0 ° C to 20 ° C, more preferably 0 ° C to 20 ° C.

[0028] The preparation method of the hydroxychloroquine sulfate may further include post-treatment, which may be a conventional post-treatment in the art, preferably filtration and drying.

[0029] Wherein said drying is conventionally dry in the art, preferably vacuum drying. The vacuum drying temperature is preferably from 50 to 80 °C.

[0030] Wherein, the purity of the hydroxychloroquine sulfate can reach >99.9%, and the

maximum single impurity is <0.06%.

[0031] In the method for preparing hydroxychloroquine sulfate, preferably the hydroxychloroquine is prepared by the following steps:

[0032] Step (1), 4,7-dichloroquinoline and hydroxychloroquine side chain compound (5-(N-ethyl-N-2-hydroxyethylenediylamino)-2-pentylamine) under inert gas protection , 134 ~ 144 ° C reaction, to 4,7-dichloroquinoline content of less than or equal to 10%, to obtain crude hydroxychloroquine; the hydroxychloroquine crude hydroxychloroquine content of > 92%;

[0033] In the step (2), the crude hydroxychloroquine obtained in the step (1) is recrystallized from a mixed solvent of an alcohol solvent and an ester solvent to obtain the hydroxychloroquine fine product.

[0034] In the step (1), the inert gas may be an inert gas conventional in the art to not participate in the reaction; in the present invention, preferably one or more of helium, argon, nitrogen and carbon dioxide. .

[0035] In the step (1), the molar ratio of the 4,7-dichloroquinoline to the hydroxychloroquine side chain compound may be 1:1.2 to 1:2, preferably 1:1.4 to 1.6 (for example, 1) :1.5).

[0036] In the step (1), the progress of the reaction can be monitored by a conventional monitoring method (for example, TLC, HPLC or NMR) in the art, and in the present invention, the content of the 4,7-dichloroquinoline is preferably 4 ~6%.

[0037] In the step (1), after the reaction of the 4,7-dichloroquinoline and the hydroxychloroquine side chain compound is completed, it is preferably cooled to 80 ° C or lower.

[0038] In the step (1), preferably, after the reaction is completed, the quenching liquid is quenched to obtain the crude hydroxychloroquine; more preferably, after the reaction is finished, the quenching liquid is quenched, and the organic solvent is extracted. Distillation, removal of the organic solvent, the crude hydroxychloroquine can be obtained.

[0039] In the step (1), the quenching liquid is preferably water or an aqueous sodium hydroxide solution having a concentration by weight of 6 to 10%, more preferably an aqueous sodium hydroxide solution having a mass percentage of 7%.

[0040] In the step (1), the amount of the quenching liquid may be a conventional amount in the art, and preferably the mass ratio of the quenching liquid to the 4,7-dichloroquinoline is 3:1.

[0041] In the step (1), the organic solvent is preferably one or more of dichloromethane, chloroform and ethyl acetate.

[0042] In the step (2), the ester solvent may be conventional in the art, and in the present invention, it is preferably an acetate solvent, more preferably methyl acetate, ethyl acetate, propyl acetate or acetic acid. One or more of propyl ester, butyl acetate and isobutyl acetate.

[0043] In the step (2), the alcohol solvent may be conventional in the art, and in the present

invention, preferably one or more of ethanol, methanol and isopropyl alcohol.

[0044] In the step (2), the mixed solvent is preferably ethanol and ethyl acetate.

[0045] In the step (2), the weight of the ester solvent and the alcohol solvent in the mixed solvent is preferably from 1:0.1 to 0.2.

[0046] In the step (2), the weight of the recrystallized mixed solvent and the crude hydroxychloroquine is preferably from 1:0.3 to 1:0.7.

[0047] In the step (2), the recrystallization may be a conventional crystal in the art, for example, after the crude hydroxychloroquine is dissolved, it is cooled to make the solution into a supersaturated state, and the product is solid precipitated; Preferably, it is after 65-75 ° C is dissolved; it is cooled to 10 ° C for crystallization.

[0048] After crystallization of the hydroxychloroquine, the hydroxychloroquine product is preferably obtained by filtration.

[0049] Preferably, the hydroxychloroquine obtained after filtration is washed with the mixed solvent.

[0050] The invention also provides a preparation method of hydroxychloroquine, comprising the following steps:

[0051] Step (1), 4,7-dichloroquinoline and hydroxychloroquine side chain compound (5-(N-ethyl-N-2-hydroxyethylenediylamino)-2-pentylamine) under inert gas protection , 134 ~ 144 ° C reaction, to 4,7-dichloroquinoline content of less than or equal to 10%, to obtain crude hydroxychloroquine; the hydroxychloroquine crude hydroxychloroquine content of > 92%;

[0052] In the step (2), the crude hydroxychloroquine obtained in the step (1) is recrystallized from a mixed solvent of an alcohol solvent and an ester solvent to obtain a hydroxychloroquine fine product.

[0053] In the step (1), the inert gas may be conventional in the art so as not to participate in the reaction, and in the present invention, preferably one or more of helium, argon, nitrogen and carbon dioxide.

[0054] In the step (1), the molar ratio of the 4,7-dichloroquinoline to the hydroxychloroquine side chain compound may be 1:1.2 to 1:2, preferably 1:1.4 to 1.6 (for example, 1) :1.5).

[0055] In the step (1), the progress of the reaction can be monitored by a conventional monitoring method (for example, TLC, HPLC or NMR) in the art, and in the present invention, the content of the 4,7-dichloroquinoline is preferably 4 ~6%.

[0056] In the step (1), after the reaction of the 4,7-dichloroquinoline and the hydroxychloroquine side chain compound is completed, it is preferably cooled to 80 ° C or lower.

[0057] In the step (1), preferably, after the reaction is completed, the quenching liquid is quenched to obtain the crude hydroxychloroquine; more preferably, after the reaction is

finished, the quenching liquid is quenched, and the organic solvent is extracted. Distillation, removal of the organic solvent, the crude hydroxychloroquine can be obtained.

[0058] In the step (1), the quenching liquid is preferably water or an aqueous sodium hydroxide solution having a concentration by weight of 6 to 10%, more preferably an aqueous sodium hydroxide solution having a mass percentage of 7%.

[0059] In the step (1), the amount of the quenching liquid may be a conventional amount in the art, and preferably the mass ratio of the quenching liquid to the 4,7-dichloroquinoline is 3:1.

[0060] In the step (1), the organic solvent is preferably one or more of dichloromethane, chloroform and ethyl acetate.

[0061] In the step (2), the ester solvent may be conventional in the art, and in the present invention, it is preferably an acetate solvent, more preferably methyl acetate, ethyl acetate, propyl acetate or acetic acid. One or more of propyl ester, butyl acetate and isobutyl acetate.

[0062] In the step (2), the alcohol solvent may be conventional in the art, and in the present invention, preferably one or more of ethanol, methanol and isopropyl alcohol.

[0063] In the step (2), the mixed solvent is preferably ethanol and ethyl acetate.

[0064] In the step (2), the weight of the ester solvent and the alcohol solvent in the mixed solvent is preferably from 1:0.1 to 0.2.

[0065] In the step (2), the weight of the recrystallized mixed solvent and the crude hydroxychloroquine is preferably from 1:0.3 to 1:0.7.

[0066] In the step (2), the recrystallization may be a conventional crystal in the art, for example, after the crude hydroxychloroquine is dissolved, it is cooled to make the solution into a supersaturated state, and the product is solid precipitated; Preferably, it is after 65-75 ° C is dissolved; it is cooled to 10 ° C for crystallization.

[0067] After crystallization of the hydroxychloroquine, the hydroxychloroquine product is preferably obtained by filtration.

[0068] Preferably, the hydroxychloroquine obtained after filtration is washed with the mixed solvent.

[0069] In the hydroxychloroquine product, the purity of the hydroxychloroquine is >99.0% by mass; preferably, the maximum single impurity is controlled within 0.06%, and the total content of the remaining impurities is <0.04%.

[0070] In the present invention, the contents of the crude hydroxychloroquine, the hydroxychloroquine, the hydroxychloroquine sulfate, and the impurities are all determined by liquid chromatography (HPLC) and the area normalization method is used.

[0071] The above preferred conditions can be arbitrarily combined without departing from the ordinary knowledge in the art, that is, preferred embodiments of the present invention.

[0072] The reagents and starting materials used in the present invention are commercially available.

[0073] In the present invention: the term "XRPD" means powder X-ray diffraction;

[0074] The term "IR" means infrared spectroscopy;

[0075] The term "DSC" means differential scanning calorimetry;

[0076] The term "HPLC" means high performance liquid chromatography;

[0077] In the present invention, if the operating temperature is not limited, it is carried out at room temperature. The room temperature is from 0 ° C to 35 ° C, preferably from 20 ° C to 30 ° C.

[0078] The positive progress of the invention is as follows: 1) The preparation method of the invention is simple, environmentally friendly and rapid, avoids the use of toxic catalyst phenol, the reaction is carried out under normal pressure, avoids the danger of high pressure reaction; 2) through crystallization, product impurities The content of the hydroxychloroquine obtained by the purification is as high as 99.9%, the maximum single impurity is controlled within 0.06%, and the total content of the remaining impurities is <0.04%; 3) the hydroxychloroquine sulfate can be further prepared by using the aqueous sulfuric acid solution, and the purity can reach 99.9%. The maximum single impurity control is within 0.06%, and the total impurity content is <0.04%.

[0079] DRAWINGS

[0080] BRIEF DESCRIPTION OF THE DRAWINGS Figure 1 is an X-ray powder diffraction pattern of hydroxychloroquine sulfate Form A prepared in Example 11 of the present invention.

[0081] 2 is a DSC chart of hydroxychloroquine crystal form A prepared in Example 11 of the present invention.

[0082] Detailed ways

[0083] The invention is further illustrated by the following examples, which are not intended to limit the invention. The experimental methods in the following examples which do not specify the specific conditions are selected according to conventional methods and conditions, or according to the product specifications.

[0084] In the following examples, the content was calculated by liquid chromatography (HPLC) and the area normalization method was used. The HPLC method is as follows:

[0085] HPLC model: Aglient 1200

[0086] Column type: Aglient Zorbax XDB-C8 4.6×150mm×5μm

[0087] Detection wavelength: 254nm

[0088] Mobile phase A: 2 mL of triethylamine and 6.8 g of KH2PO4 were dissolved in 900 mL of water, and pH = 8.0 was adjusted with 1 mol/L KOH. Dilute to 1000 mL and mix well;

[0089] Mobile phase B: methanol;

[0090] Gradient elution:

[0091] Time A(%) B(%) Description 0min 53 47 Equivalence 20min 33 67 Equivalence 20.1min 53 47 Isocratic 30min 53 47 Isocratic

[0092] The model of the powder X-diffraction test instrument according to the present invention is Bruker D8ADVANCE; the test conditions are: Voltage, Current is 40Kv, 40 mA, Stand-End Position is 0-40° 2θ, Increment is 0.02° 2θ, Time per step is 0.5 s. Detection environment: 26 ° C, humidity 44% RH.

[0093] The differential scanning calorimeter model of the present invention is TA DSC Q2000; the test method is: Equlibrate at 20 ° C, Ramp at 10.0 ° C/min to 250.0 ° C, N 2 flow is 40 mL / min, aluminum pan, capped. Detection environment: 25 ° C, humidity 55% RH.

[0094] Examples 1-8

[0095] Step (1), preparation of crude hydroxychloroquine

[0096] Add 4,7-dichloroquinoline (100g) and side chain to the reaction flask, stir under nitrogen, raise to a certain temperature, and react to HPLC to detect 4,7-dichloroquinoline content below 6%, stop The reaction was quenched with a quenching liquid, and extracted with an organic solvent. The extract was washed with purified water to pH 7-8, and distilled under reduced pressure to give crude chlorochloroquine.

[0097] Table 1. Preparation of crude hydroxychloroquine

[0098]

[0099] Step (2), preparation of hydroxychloroquine

[0100] The mixed solvent is added to the crude product obtained in the step (1), dissolved under the conditions of 70±5° C., cooled, cooled to 10° C., seeded, crystallized, suction filtered, and dried to obtain a hydroxychloroquine boutique.

[0101] Table 2. Preparation of hydroxychloroquine

[0102]

[0103]

[0104] Comparative Example 1:

[0105] 100g side chain, 112g 4.7-dichloroquinoline was added to a three-necked flask, protected by nitrogen, heated to 100 ° C, stirred for 1 h, then heated to 120-130 ° C for 20 h, after the reaction was completed, the temperature was lowered (below 80 ° C), with

hydroxide The sodium solution was adjusted to pH > 12, extracted with dichloromethane, washed with water until neutral, and dichloromethane was evaporated under reduced pressure to give 147 g of crude chlorochloroquine. The yield was 86.6%, and the HPLC purity was 90.47%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 20 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.80%, a maximum single impurity of 0.12%, and a yield of 88.2%.

[0106] Comparative Example 2

[0107] 100g of 4,7-dichloroquinoline and 110g of side chain were added to the reactor, protected by nitrogen, heated at 78 ° C to dissolve 4,7-dichloroquinoline, heated at 120 ° C for 20 minutes, and heated to 140 ° C. After the reaction is completed, the reaction solution is cooled to 90 ° C ~ 100 ° C, 5% sodium hydroxide solution is added, alkalized to neutral, extracted with dichloromethane, and added to the combined organic phase, 250 g of drinking water is added. The layering was repeated until the pH of the washing water was 7, and methylene chloride was distilled off under reduced pressure to give 164 g of crude hydroxy chloroquine. The yield was 96.9%, and the HPLC purity was 91.78%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.70%, a maximum single impurity of 0.21%, and a yield of 75.3%.

[0108] Comparative Example 3

[0109] a. Preparation of hydroxychloroquine

[0110] 100g of 4,7-dichloroquinoline and 110g of side chain were added to the reactor, protected by nitrogen, heated at 78 ° C to dissolve 4,7-dichloroquinoline, heated at 120 ° C for 20 minutes, and heated to 140 ° C. After the reaction is completed, the temperature is lowered (below 80 ° C), the pH is adjusted to 12 with sodium hydroxide solution, extracted with dichloromethane, washed with water until neutral, and dichloromethane is evaporated under reduced pressure to give crude chlorochloroquine 146 g, yield: 86.7%. The HPLC purity was 90.49%. Add 400g of isopropyl acetate to the crude hydroxychloroquine, then add 5.0g of activated carbon, reflux at elevated temperature for 1 hour, heat filtration, the filtrate is cooled to 0 ° C, crystallization for 2 h, filtered, and dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product. . The purity was 99.63%, the maximum single impurity was 0.091%, and the yield was 88.1%.

[0111] b. Preparation of hydroxychloroquine sulfate

[0112] 100 g of hydroxychloroquine obtained in the previous step was dissolved in 500 g of absolute ethanol, concentrated sulfuric acid was added dropwise at 25 ° C until the solution became cloudy, the temperature was raised at 50 ° C for 9 hours, cooled to 20 ° C for 1 h, and filtered to obtain hydroxychloroquine sulfate, purity 99.74. %, the largest single impurity 0.17%, the yield was 90.2%.

[0113] Comparative Example 4

[0114] a. Preparation of hydroxychloroquine

[0115] 100g of 4,7-dichloroquinoline and 110g of side chain were added to the reactor, protected by nitrogen, heated at 78 ° C to dissolve 4,7-dichloroquinoline, heated at 120 ° C for 20 minutes, and heated to 140 ° C. After the reaction is completed, the temperature is lowered (below 80 ° C), adjusted to pH > 12 with sodium hydroxide solution, extracted with dichloromethane, washed with water until neutral, and dichloromethane is evaporated under reduced pressure to give crude hydroxychloroquine 149 g, yield 87.8%. The HPLC purity was 90.91%. To the crude hydroxychloroquine, 300 g of ethyl acetate was added, and the mixture was heated to dissolve, and the temperature was lowered to 0 to 10 ° C. After incubation for 2 hours, the mixture was filtered and dried to obtain a hydroxychloroquine dry product. The purity was 99.63%, the maximum single impurity was 0.095%, and the yield was 89.6%.

[0116] b. Preparation of hydroxychloroquine sulfate

[0117] 100g of hydroxychloroquine obtained in the previous step is dissolved in 500g of absolute ethanol, concentrated sulfuric acid is added dropwise at 25 °C until the solution is cloudy, heated at 50 ° C for 9 hours, cooled to 20 ° C for 1 h, and filtered to obtain hydroxychloroquine sulfate, purity 99.79 %, the largest single impurity is 0.18%, and the yield is 89.2%.

[0118] Comparative Example 5

[0119] In a three-necked round bottom flask, 4,7-dichloroquinoline (198 g, 1.0 mol), hydroxychloroquine side chain (182 g, 1.05 mol) and isopropyl acetate 1089 g were added, and sodium ethoxide (13.6 g, 0.2 mol) was slowly added. The temperature is slowly raised to reflux under stirring conditions, and then isopropyl acetate is distilled off, and the temperature is gradually raised to 110 ° C over 9 hours, then heated to 120-122 ° C for 10 hours, and finally heated at 120-122 ° C for 4 hours, until the reaction is complete. Thereafter, the reaction solution was cooled to 90 to 100 ° C, directly added to a 5% sodium hydroxide solution, and alkalized to neutrality. The distilled isopropyl acetate was extracted twice, and the layers were separated. 500 g of drinking water was added to the combined organic phase, washed, layered, and the above operation was repeated until the pH of the washing water was 7. After the washing was completed, the water temperature was controlled to 65 ° C, and isopropyl acetate was distilled off under reduced pressure to obtain crude hydroxychloroquine. The HPLC purity was 91.78%. To the crude hydroxychloroquine, 300 g of methyl ethyl ketone and 300 g of ethyl acetate were added, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxychloroquine. The wet product was dried at 60 ° C for 4 h to obtain hydroxychloroquine dry product with a purity of 99.8%, a maximum single impurity of 0.17%, and a yield of 87.6%.

[0120] Comparative Example 6

[0121] 20g side chain, 22.4g 4.7-dichloroquinoline was added to a three-necked flask, protected by nitrogen, heated to 100 ° C, stirred for 1 h, then heated to 120-130 ° C for 20 h,

the reaction was completed, slightly cooled (90 ° C ~ 100 ° C) 20 g of water was added to the reaction solution, and 40 g of concentrated hydrochloric acid was added. After stirring, 80 g of liquid alkali was added, and the mixture was stirred for 30 minutes. The aqueous phase was discarded, and the organic solvent was evaporated under reduced pressure to obtain a crude product. HPLC purity was 90.2%. The crude product was added with 300 g of methyl ethyl ketone and 300 g of ethyl acetate, and the mixture was heated at 75 ° C to dissolve. After 4 h, the temperature was slowly lowered to 10 ° C, filtered, and the filter cake was washed with a mixed solvent of methyl ethyl ketone and ethyl acetate to obtain hydroxy chloroquine wet product, 60 ° C. The dried hydroxychloroquine was dried for 4 h, the purity was 99.80%, the maximum single impurity was 0.13%, and the yield was 88.2%.

[0122] Comparative Example 7

[0123] 100 g of crude hydroxychloroquine (HPLC purity greater than 92%) obtained in Example 1 was placed in a single-mouth bottle, and a mixed solvent of 260 g of ethyl acetate and 40 g of isopropyl alcohol was added thereto, and the mixture was stirred at a temperature, and slowly heated to 80 ° C, refluxing 1 After the hour, the temperature is lowered to 15-20 ° C, the crystallization time is started for 5 hours, the temperature is lowered to 0 to 5 ° C, the crystal is separated by filtration, and the filter cake is washed with ethyl acetate to obtain hydroxychloroquine wet product, which is dried to obtain fine hydroxychloroquine. The HPLC purity was 99.7%, the maximum single impurity was 0.16%, and the yield was 75%.

[0124] Comparative Example 8

[0125] 100 g of crude hydroxychloroquine (HPLC purity greater than 92%) obtained in Example 1 was placed in a single-mouth bottle, and a mixed solvent of 260 g of ethyl acetate and 40 g of isopropyl alcohol was added thereto, and the mixture was stirred and dissolved at a temperature. After completely dissolved, 4.2 g was added. Activated carbon, slowly warmed to 80 ° C, reflux for 1 hour, hot filtered, filter cake washed with 26g of ethyl acetate and 4g of isopropanol mixed solvent, the filtrate was combined, cooled to 15 ~ 20 ° C, began crystallization time 5 hours, cooling to 0 to 5 ° C, after thermal crystallization, filtration, the filter cake was washed with ethyl acetate to obtain hydroxy chloroquine wet product, which was dried to obtain HPLC hydroxychloroquine with a purity of 99.8%, a maximum single impurity of 0.11%, and a yield of 70%.

[0126] Comparison of Example 1 and Comparative Examples 3 and 4

[0127] Table 3. Comparison of products and impurities in crude hydroxychloroquine

[0128]

[0129] Table 4. Comparison of products and impurities in hydroxychloroquine

[0130]

[0131]

[0132] Note: The relative retention time is based on the hydroxychloroquine HPLC retention time; that is, the relative retention time of "1" indicates hydroxychloroquine, and the other relative retention times are impurities.

[0133] After refining, in Example 1, the content of impurity 1 was controlled to be <0.06%; the content of the remaining impurities was one order of magnitude lower than that of the comparative example, and the total amount of remaining impurities was <0.04%. The main impurity content in the comparative example was 0.085-0.1%, both of which were close to 0.1%. The impurity content could not be stably controlled, and it was easy to be >0.1% in the subsequent storage process.

[0134] Examples 9 to 17 and Comparative Examples 9 to 11

[0135] Preparation of Hydroxychloroquine Sulfate - Salt Crystallization

[0136] Hydroxychloroquine (50 g; obtained in Example 1) was dissolved in an alcohol solvent, and an aqueous sulfuric acid solution was added dropwise at 20 to 35 ° C to turbidity, and the dropwise addition was stopped, and the temperature was raised to 35 to 55 ° C, and the reaction was kept for 5 hours or more. After the reaction was completed, the temperature was lowered to 0 to 20 ° C, and the temperature was kept for 1 hour, and the filter cake was filtered by suction to obtain a finished product.

[0137] Table 5. Preparation of hydroxychloroquine sulfate

[0138]

[0139]

[0140] The HPLC data of Example 11 and Comparative Example 9 were analyzed as follows:

[0141] Table 6. Comparison of products and impurities in hydroxychloroquine sulfate

[0142]

[0143] Note: The relative retention time is based on the HPLC retention time of hydroxychloroquine sulfate; that is, the relative retention time is “1” for hydroxychloroquine sulfate, and the other relative retention time is impurity.

EP0588430A1
(S)-(+)-Hydroxychloroquine
[PDF]

Abstract
The present invention provides (S)-(+)-Hydroxychloroquine substantially free of (R)-(-)-hydroxychloroquine, or a pharmaceutically acceptable acid-addition salt thereof, the use in the manufacture of a medicament for treatment of malaria, lupus erythematosus or rheumatoid arthritis and a composition containing it for the treatment of such diseases. The weight ratio of (S)-(+)-Hydroxychloroquine to (R)-(-)-hydroxychloroquine is preferably at least 90:10, most preferably at least 98:2.

0001] The invention relates to (S)-(+)-2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol [hereinafter (S)-(+)-hydroxychloroquine] which

is useful in the treatment of acute attacks and suppression of malaria due to Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and susceptible strains of Plasmodium falciparum, systemic and discoid lupus erythematosus, and rheumatoid arthritis.

[0002] Racemic hydroxychloroquine, which is 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol (Surrey U.S. Patent 2,546,658), and which is sold as the sulfate salt by Sanofi Winthrop Pharmaceuticals under the tradename Plaquenil® Sulfate, is primarily useful as an antimalarial agent and is also used in treating lupus erythematosus and rheumatoid arthritis.

[0003] A.J. McLachlan et al ., J. Chromatogr., 570 (No. 1), 119-127, September 18, 1991, disclose the high-performance liquid chromatographic separation of the enantiomers of hydroxychloroquine and its major metabolites in biological fluids. The authors acknowledge a gift of S(+)-hydroxychloroquine from Sterling Pharmaceuticals.

[0004] J. Iredale et al. , J. Chromatogr., 573 (No. 2), 253-258, January 17, 1992, disclose the development of a sequential achiral-chiral high-performance liquid chromatographic system for the determination of the enantiomers of hydroxychloroquine and its three major metabolites.

[0005] S.E. Tett et al ., Br. J. Clin. Pharmac., 26 , 303-313 (1988), disclose a dose-ranging study of the pharmacokinetics of racemic hydroxychloroquine following intravenous administration to healthy volunteers. The authors state that the pharmacokinetics of hydroxychloroquine are similar to those of chloroquine.

[0006] Chem. Abstr. 92 , 69587p (1980) discloses that when administered orally daily for four days beginning at two hours after Plasmodium bergher infestation in mice, doses of 5 and 20 mg/kg of the d-enantiomer of chloroquine diphosphate were more effective than corresponding doses of the 1-enantiomer in antimalarial parameters measured, including percentage of cured mice at >7.5 mg/kg; and that the d-enantiomer was also more active than the racemate, but only at subcurative doses.

[0007] Chem. Abstr. 90 , 132863b (1979) discloses the results of a study of the activity of chloroquine enantiomers against rodent malaria in which it was found that (+)-chloroquine diphosphate was a more active antiplasmodial agent than (—)-chloroquine diphosphate in Plasmodium vinckei-infected mice, and that the activity of (±)-chloroquine diphosphate was between that the the two enantiomers.

[0008] J.C. Craig et al ., J. Org. Chem., 53 , 1167-1170 (1988), disclose the absolute configuration of the enantiomers of chloroquine and the synthesis of (R)-(—)-chloroquine by condensation of (R)-(—)-4-amino-1-(diethylamino)pentane of >90% purity with 4,7-dichloroquinoline.

[0009] G. Blaschke et al. , Chem. Ber., 111 , 2732-2734 (1978) disclose the chromatographic separation of the enantiomers of chloroquine as well as their preparation by condensation of (+)- and (—)-4-amino-1-(diethylamino)pentane with 4,7-dichloroquinoline.

[0010] H.N. Bernstein, Annals of Ophthalmology, 23 , 292-296 (1991), presents an analysis of all published cases and Food and Drug Administration reports of retinopathy induced by hydroxychloroquine. The author states that antimalarial therapy, because of a relative lack of

systemic side effects compared with other immunomodulating drugs, has been used increasingly over the past 15 years for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and other predominantly autoimmune diseases, and that in the United States, hydroxychloroquine is preferred to chloroquine because it is considered significantly less retinotoxic at the current recommended maximum dose (400 mg/day, according to the FDA and the manufacturer). The author nevertheless notes that physicians are concerned about using drugs with retinotoxic potential at higher dose levels. He then suggests, inter alia , that the risk of true retinopathy is nullified when the maintenance daily dose is based on ≦6.5 mg/kg body weight and states that even in the absence of a real toxicity risk, it is recommended that a periodic ocular examination program be followed because of the retinotoxic history associated with hydroxychloroquine.

[0011] Drugs having an asymmetric center are, in most instances, administered as racemates consisting of a 1:1 mixture of two enantiomers. However, since there often are pharmacodynamic and pharmacokinetic differences between the two enantiomers, therapeutic efficacy may reside entirely or for the most part in one of the two enantiomers and therefore may be diluted by the other enantiomer in the racemate and, moreover, any adverse effect which may be associated with the racemate may be attributable to the other enantiomer. In such cases it would be desirable to administer the single enantiomer in which the therapeutic efficacy resides.

[0012] Plaquenil® Sulfate (hydroxychloroquine sulfate) is a racemic mixture (1:1) of 2 enantiomers. The manufacturer of this drug contraindicates its use, inter alia , in the presence of retinal or visual field changes attributable to any 4-amino-quinoline compound and warns that irreversible retinal damage has been observed in some patients who had received long term or high-dosage 4-aminoquinoline therapy for discoid and systemic lupus erythematosus or rheumatoid arthritis and notes that retinopathy has been reported to be dose-related. Adverse reactions discussed by the manufacturer include a small number of cases of retinal changes which have been reported as occurring in patients who received only hydroxychloroquine.

[0013] Although Plaquenil® Sulfate has an excellent ocular safety record when the maintenance dose levels recommended by the manufacturer (310 mg base/day) for the treatment of malaria, discoid and systemic lupus erythematosus and rheumatoid arthritis are not exceeded, nevertheless, because cases of retinal changes in patients receiving only hydroxychloroquine have been reported and physicians are concerned about using drugs with retinotoxic potential at higher doses (see H.N. Bernstein, supra), it would be highly desirable if the risk of retinopathy in the use of hydroxychloroquine could be substantially reduced, particularly for that segment of the population which could benefit from hydroxychloroquine therapy but where such therapy is contraindicated because of the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound.

[0014] Unexpectedly, it has now been found that when (S)-(+)-hydroxychloroquine and its (R)-(—)-antipode were compared in the Rat Pleurisy Macrophage Model, which model is used to identify disease modifying antirheumatic drugs [see Z.E. Mielens et al ., J. Rheumatol., 12 , 1083-1087 (1985)], (S)-(+)-hydroxychloroquine was approximately 70% more active than the corresponding (R)-(—)-enantiomer in decreasing the accumulation of cells (monocytes) to the pleural cavity. Furthermore, it was found that in a study wherein racemic hydroxychloroquine was administered either intravenously, subcutaneously or orally to rabbits, there was an enantioselective accumulation of (R)-(—)-hydroxychloroquine in the

ocular tissue. The ratio of the (R)-(—)-enantiomer to the (S)-(+)-enantiomer in this study was 1.58 ± 0.24. These results were consistent with the results of pharmacokinetic studies in humans treated with racemic hydroxychloroquine in which it was found that for (R)-(—)-hydroxychloroquine, the fraction absorbed was approximately two times greater, the systemic clearance was more than two fold greater and the apparent half life was significantly faster than for the corresponding (S)-(+)-enantiomer. These differences are attributed to enantioselective distribution into various tissue compartments such as the retina.

[0015] These unexpected discoveries have important clinical implications for hydroxychloroquine therapy in that malaria, lupus erythematosus and rheumatoid arthritis may now be effectively treated with (S)-(+)-hydroxychloroquine substantially free of (R)-(—)-hydroxychloroquine with concomitant lower adverse effects attributable to the corresponding (R)-(—)-enantiomer with the result that it will be possible, where indicated, to administer (S)-(+)-hydroxychloroquine at higher dose levels and/or longer periods of times than is now recommended for administration of equivalent dose levels of racemic hydroxychloroquine.

[0016] Therefore, in one aspect of the invention there is provided (S)-(+)-hydroxychloroquine substantially free of (R)-(—)-hydroxychloroquine, or a pharmaceutically acceptable acid-addition salt thereof.

[0017] In another aspect there is provided a method for the treatment of malaria, lupus erythematosus or rheumatoid arthritis in a human which comprises administering to the human an amount effective to treat malaria, lupus erythematosus or rheumatoid arthritis of (S)-(+)-hydroxychloroquine substantially free of (R)-(—)-hydroxychloroquine or a pharmaceutically acceptable acid-addition salt thereof.

[0018] In another aspect the invention provides a composition for treating malaria, lupus erythematosus or rheumatoid arthritis in a human comprising (S)-(+)-hydroxychloroquine substantially free of (R)-(—)-hydroxychloroquine or a pharmaceutically acceptable acid-addition salt thereof in an amount effective for the treatment of malaria, lupus erythematosus or rheumatoid arthritis and a pharmaceutically acceptable vehicle.

[0019] A further aspect of the invention provides the use in the manufacture of a medicament for treating malaria, lupus erythematosus or rheumatoid arthritis in a human of (S)-(+)-hydroxychloroquine substantially free of (R)-(—)hydroxychloroquine, or a pharmaceutically acceptable acid-addition salt thereof. The (S)-(+)-hydroxychloroquine substantially free of (R)-(—)-hydroxychloroquine, or a pharmaceutically acceptable acid-addition salt thereof, is preferably present in the medicament in therapeutic amounts effective for the treatment of such diseases.

[0020] In order to avoid or minimize adverse effects associated with the enantioselective accumulation of (R)-(—)-hydroxychloroquine in ocular tissue, it is preferable in practising the invention to use as the active ingredient (S)-(+)-hydroxychloroquine substantially free of (R)-(—)-hydroxychloroquine. In this context, the expression "substantially free" means that the active ingredient should contain at least 90% by weight of (S)-(+)-hydroxychloroquine and 10% by weight or less of (R)-(—)-hydroxychloroquine, preferably at least 95% by weight of the (S)-(+)-enantiomer and 5% by weight or less of the (R)-(—)-enantiomer and more preferably at least 98% by weight and 2% by weight or less of the (R)-(—)-enantiomer. Ideally the (S)-(+)-hydroxychloroquine should be free of (R)-(—)-hydroxychloroquine.

[0021] Included within the purview of this invention in addition to (S)-(+)-hydroxychloroquine are its pharmaceutically acceptable acid-addition salts such as those derived from nontoxic inorganic acids, including hydrochloric acid, sulfuric acid, sulfamic acid and the like, and nontoxic organic acids, including tartaric acid, citric acid, acetic acid and the like.

[0022] The composition of the invention can be formulated for oral or parenteral administration in solid, liquid or other appropriate dosage forms including tablets, capsules and solutions, using conventional pharmaceutically acceptable vehicles and techniques. The invention will now be described with reference to the following Example but is in no way to be construed as limited thereto.
EXAMPLE Preparation of (S)-(+)-Hydroxychloroquine

[0023] (S)-(+)-Hydroxychloroquine was prepared by condensing (S)-(+)-2-[(4-aminopentyl)ethylamino]ethanol with 4,7-dichloroquinoline. The latter compound is known. The (S)-(+)-2-[(4-aminopentyl)ethylamino]ethanol was prepared by resolving known racemic 2-[(4-aminopentyl)ethylamino]ethanol by forming a salt thereof with known (S)-(+)-mandelic acid and separating the (S)-(+)-mandelic acid salts of the two enantiomers by crystallization.

[0024] The following example illustrates the method of preparation.
a) (S)-(+)-2-[(4-Aminopentyl)ethylamine]ethanol.

[0025] A solution of (S)-(+)-mandelic acid (15.9 g, 105 mmol, 0.60 equivalents) in ethyl alcohol was added to a solution of racemic 2-[(4-aminopentyl)ethylamino]ethanol (30.37 g, 174 mmol, 1.00 equivalents) in ethyl ether. The solvents were evaporated and the resulting white solid was recrystallized from ethyl alcohol, washed with a little ethyl ether, recrystallized again from ethyl alcohol and washed with a little ethyl alcohol and then ethyl ether. The crystals were dried in vacuo overnight to give 7.45 g of salt of the title compound with (S)-(+)-mandelic acid, m.p. 126-127°C. This salt was dissolved in water and the resulting solution was made basic with 35% sodium hydroxide and extracted three times with methylene chloride. The combined extracts were dried (K_2CO_3), filtered and evaporated. The residue was distilled (Kugelrohr; 80-100°C/0.020 tort) to yield the title compound as a colorless oil (approximately 3.7 g) which was used as such in the next step.
b) (S)-(+)-Hydroxychloroquine.

[0026] A mixture of the product from (a) above (approximately 3.7 g, 19.0 mmol, 1.00 equivalents). N-ethyldiisopropylamine (2.45 g, 20.9 mmol, 1.10 equivalents) and 4,7-dichloroquinoline (3.31 g, 19.0 mmol, 1.00 equivalents) was heated at reflux under nitrogen for 48 hours and cooled. The excess base was poured off and the residue was taken up in methyl alcohol and excess aqueous sodium hydroxide. The mixture was diluted with water and extracted three times with methylene dichloride. The combined organic extracts were washed two times with water, once with brine, dried (K_2CO_3), filtered and evaporated to dryness. The residue was filtered through silica gel with tetrahydrofuran:diethylamine (95:5) to give 4.12 g of material. This material was subjected to fractional distillation (Kugelrohr). A white crystalline solid was obtained at approximately 130°C and 0.010 torr. The receiver bulb was changed and the distillation temperature was increased to approximately 200°C. This provided 2.93 g of the title compound which was converted to its sulfate salt by treatment with one equivalent of 1 molar sulfuric acid in methyl alcohol and evaporation to a sticky oil. The oily salt was dissolved in 5 ml methyl alcohol and acetone was added slowly until the solution turned a little murky. This solution was allowed to stand overnight at room

temperature and the resulting crystalline salt was collected and washed with acetone and dried at 50°C (0.01 torr) for twenty-four hours to give approximately 390 mg of (S)-(+)-hydroxychloroquine sulfate as an off-white solid, m.p. 235-238°C(dec.); [α]D = +105.9 (1% in H_2O). It was determined by direct chromatographic resolution via high performance liquid chromatography using a chiral stationary phase that this material contained 98.4% by weight of the (S)-(+)-enantiomer and 1.6% by weight of the (R)-(—)-enantiomer.

CN109280029
Preparation method of hydroxychloroquine sulfate
[PDF]

Abstract
The invention discloses a preparation method of high-purity hydroxychloroquine sulfate. The method uses 4,7-dichloroquinoline and hydroxychloroquine side chain as raw materials to directly prepare hydroxychloroquine hydrochloride, hydroxychloroquine hydrochloride is neutralized with sodium alcoholate or potassium alcoholate, filtered, concentrated, beaten and crystallized to obtain hydroxychloroquine refined product, and the hydroxychloroquine refined product finally is subjected to salifying reaction with sulfuric acid in a certain proportion of pure aqueous solution to obtain hydroxychloroquine sulfate. The method avoids the use of phenol or its catalyst in the process of preparing hydroxychloroquine, avoids the extraction operation in the post-treatment, has high product purity, and basically does not generate waste water in the production process. The method is convenient to operate and has high yield, the HPLC purity of prepared hydroxychloroquine sulfate is more than or equal to99.6%, and maximum single impurity is less than or equal to 0.1%, and that method is more suitable for industrial production.

[0002] The invention belongs to the technical field of medicinal chemistry, and in particular relates to a preparation method of hydroxychloroquine sulfate.

[0003] Background technique

[0004] Hydroxychloroquine Sulfate, chemical name 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol sulfate is a quinoline drug, clinical For rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus, and skin lesions caused or exacerbated by sunlight.

[0005] Chinese patent CN 103724261B discloses an industrialization method of hydroxychloroquine sulfate: the temperature reaction is directly added to the side chain of 4,7-dichloroquinoline and hydroxychloroquine under the protection of inert gas, and the reaction is gradually heated to 120-130 ° C during the reaction. After 13-24 hours, the reaction is completed, the temperature is lowered, water is added to the reaction system to dissolve, and the alkalization layer is separated, the aqueous phase is discarded, and the organic phase is crystallized by adding an organic solvent to obtain hydroxychloroquine. In the method, hydroxychloroquine is easily precipitated as an oil during the acid-base treatment, and a large amount of alkali and inorganic salts are easily mixed, so that the purity of the crude hydroxychloroquine is not high, and the quality of hydroxychloroquine sulfate obtained directly for salt formation is often unqualified.

[0006] Chinese patent CN104230803B provides a preparation method of hydroxychloroquine

sulfate, which dissolves 4,7-dichloroquinoline and hydroxychloroquine side chain in an acetate solvent, and adds sodium alkoxide as a catalyst to gradually heat up the acetate solvent by distillation. The condensation reaction is carried out in a manner, and after the reaction is completed, the pH is adjusted to 9-10 by adding a 5% aqueous sodium hydroxide solution, extracted with an organic solvent of an acetate, washed, crystallized to obtain hydroxychloroquine, and then a mixture solvent of hydroxychloroquine and sulfuric acid in an alcohol-water mixture is obtained. The salt formation reaction is carried out in the system. In comparison, the method described in this patent is simpler, and its main disadvantage is that the solubility of hydroxychloroquine in the acetate solvent is small, and the solvent required for extracting hydroxychloroquine using an acetate solvent in the post-treatment is used. Great amount.

[0007] In the preparation method of the above-disclosed hydroxychloroquine sulfate, there are some disadvantages which are not favorable for industrial production. Therefore, it is necessary to solve the above problems and further improve the synthesis process of hydroxychloroquine sulfate.

[0008] Summary of the invention

[0009] The object of the present invention is to overcome the above problems and to provide a novel green environmentally friendly, simple and convenient method for synthesizing high-purity hydroxychloroquine sulfate.

[0010] The invention provides a preparation method of hydroxychloroquine sulfate, and the specific steps are as follows:

[0011] (1)After mixing 4,7-dichloroquinoline with hydroxychloroquine side chain, the mixture is heated and condensed without solvent and without catalyst to prepare hydroxychloroquine hydrochloride;

[0012] (2)Hydroxychloroquine hydrochloride is dissolved in an anhydrous alcohol solvent, neutralized with sodium alkoxide or potassium alkoxide, and the resulting potassium chloride or sodium chloride is removed by filtration, and the filtrate is concentrated to obtain crude hydroxychloroquine;

[0013] (3)The crude hydroxychloroquine is firstly pretreated with acetate and then crystallized with a mixed solvent of acetate and alcohol to obtain a hydroxychloroquine product having a purity greater than 99.5% and a maximum single impurity of less than 0.1%;

[0014] (4)The hydroxychloroquine product is dissolved in ethanol, and an equimolar aqueous solution of sulfuric acid or an ethanol-water solution of sulfuric acid is added dropwise thereto, and the internal temperature of the reaction is controlled to be below 40 ° C during the dropwise addition, and the mixture is stirred at room temperature after the dropwise addition. 10-24h, filtration, drying, that is, hydroxychloroquine sulfate, its HPLC purity>99.6%, the maximum single impurity <0.1%; the reaction equation is as follows:

[0015]

[0016] In the above step (1), the molar ratio of the 4,7-dichloroquinoline to the

hydroxychloroquine side chain is 1:1 to 1:1.2; the reaction temperature is 110-130 ° C, and the reaction time is 18-48 h.

[0017] In the above step (2), the alcohol solvent is selected from any one or more of methanol, ethanol or isopropanol; and the sodium alkoxide or potassium alkoxide reagent is selected from the group consisting of sodium methoxide, sodium ethoxide and sodium isopropoxide. Any one of sodium t-butoxide, potassium methoxide, potassium ethoxide, potassium propoxide or potassium t-butoxide.

[0018] In the above step (2), the volume-to-mass ratio of the theoretical yield of the alcohol solvent and hydroxychloroquine hydrochloride is 3-8 mL/g.

[0019] In the above step (2), the molar ratio of the amount of sodium alkoxide or potassium alkoxide added to the theoretical yield of hydroxychloroquine hydrochloride is from 1.0:1 to 1.1:1.

[0020] In the above step (3), the acetate is selected from any one of methyl acetate, ethyl acetate, isopropyl acetate or t-butyl acetate; the alcohol is selected from the group consisting of methanol, ethanol, propanol and isopropyl alcohol. Any of alcohol or n-butanol.

[0021] In the above step (3), the volume ratio of the acetate to the alcohol is from 4:1 to 8:1.

[0022] In the above step (4), the mass concentration of the aqueous solution of sulfuric acid or the ethanol-water solution of sulfuric acid is less than 35%.

[0023] The 4,7-dichloroquinoline and hydroxychloroquine side chains used in the present invention are industrial raw materials which are commercially available on a large scale, and the solvents used are industrial raw materials.

[0024] The "hydroxychloroquine side chain" referred to in the present invention means the starting material "5-(N-ethyl-N-2-hydroxyethylamine-2-pentylamine); "sodium alkoxide" means an alkyl alcohol A base formed by substituting hydrogen for sodium; "acetate" means an ester of acetic acid with a monohydric alcohol.

[0025] Compared with the prior art, the beneficial effects of the present invention are:

[0026] 1)4，7- The condensation of dichloroquinoline with the hydroxychloroquine side chain is a solventless reaction, avoiding the use of highly polluting catalyst phenol, and does not require the use of other catalysts. The reaction is carried out under normal pressure and does not require protection with an inert gas. simple.

[0027] 2)After the reaction, the anhydrous alcohol is used as a solvent to dissolve hydroxychloroquine hydrochloride, neutralized with sodium alkoxide and potassium alkoxide, and the resulting inorganic salt, sodium chloride and potassium chloride can be removed by filtration, concentrated to recover alcohol solvent, and then acetic acid. The ester solvent is beaten to obtain crude hydroxychloroquine. The extraction operation is avoided, no waste water is generated, and the labor intensity is greatly reduced.

[0028] 3)The crude hydroxychloroquine which has been subjected to acetate-based beating has a high purity, and is further crystallized by a mixed solvent of an acetate and an alcohol,

and the purity of the obtained hydroxychloroquine is further improved, and the content of the single impurity is easily reduced to 0.1% or less.

[0029] 4)Hydroxychloroquine and sulfuric acid salt are formed in an ethanol-water mixed solvent, avoiding the risk of producing toxic substances under anhydrous conditions, the product has good crystallinity, and the obtained quality index of hydroxychloroquine sulfate (HPLC purity is 99.6% or more, the largest single Miscellaneous less than 0.1%)

[0030] Detailed ways

[0031] The preparation of the hydroxychloroquine sulfate industrialization of the present invention is further illustrated and explained below by way of examples without limiting the scope of the invention.

[0032] Example 1 Synthesis of Hydroxychloroquine

[0033] In a 500 mL four-necked flask, 4,7-dichloroquinoline: 100 g (0.51 mol) and hydroxychloroquin side chain: 89 g (0.51 mol), heated to 110 ° C for 1 hour, and then heated to 120 ° C for 24 hours. The plate was monitored until the 4,7-dichloroquinoline disappeared. The mixture was cooled slightly. Anhydrous methanol (600 mL) was added, stirred and dissolved. 1.0 eq of sodium methoxide (27.5 g) was added in portions, stirred for 2 h, filtered to remove insolubles, filtrate It was concentrated to dryness under reduced pressure, and then ethyl acetate (300 mL) was added and then filtered to afford 169 g of crude chlorochloroquine.

[0034] The above crude hydroxychloroquine was added to a mixed solvent of methanol-methyl acetate (1:4, v/v, 600 mL), dissolved by heating, and then naturally cooled to room temperature, stirred and crystallized for 5 h, filtered, and the filter cake was run with methyl acetate. Washing, drying at 50 ° C to constant weight, hydroxychloroquine product about 145g, yield of 85.1%, HPLC purity > 99.5%, the maximum single impurity <0.1%.

[0035] Example 2 Synthesis of Hydroxychloroquine

[0036] In a 500 mL four-necked flask, 4,7-dichloroquinoline: 100 g (0.51 mol) and hydroxychloroquin side chain: 92 g (0.53 mol), heated to 110 ° C for 1 hour, and then heated to 125 ° C for 20 hours. The plate was monitored until 4,7-dichloroquinoline disappeared, cooled to room temperature, dissolved in ethanol (800 mL), 1.1 eq sodium ethoxide (38.15 g) was added in portions, stirred for 1-2 h, filtered to remove insolubles, and the filtrate was reduced. The mixture was concentrated to dryness, then EtOAc EtOAc (EtOAc)

[0037] The above crude hydroxychloroquine was added to a mixed solvent of ethanol-ethyl acetate (1:5, v/v, 800 mL), dissolved by heating, and then naturally cooled to room temperature, stirred and crystallized for 8 hours, filtered, and the filter cake was isopropyl acetate. Rinse, dry at 50 ° C to constant weight, hydroxychloroquine product about 146g, yield of 86.0%, HPLC purity > 99.5%, the largest single impurity <0.1%.

[0038] Example 3 Synthesis of Hydroxychloroquine

[0039] In a 500 mL four-necked flask, 4,7-dichloroquinoline: 100 g (0.51 mol) and hydroxychloroquine side chain: 95 g (0.55 mol), heated to 110 ° C for 1 hour, and then heated

to 130 ° C for 18 hours. The plate was monitored until 4,7-dichloroquinoline disappeared, cooled to room temperature, dissolved in absolute ethanol (1000 mL), 1.05 eq of potassium t-butoxide (59.9 g) was added in portions, stirred for 1-2 h, filtered to remove insoluble The filtrate was concentrated to dryness under reduced pressure, and then ethyl acetate was added and then filtered to afford crude hydroxy chloroquine (167.9 g).

[0040] The above crude hydroxychloroquine was added to a mixed solvent of ethanol-ethyl acetate (1:6, v/v, 1000 mL), dissolved by heating, and then naturally cooled to room temperature, stirred and crystallized for 6 h, filtered, and the filter cake was evaporated with ethyl acetate. Washing, drying at 50 ° C to constant weight, hydroxychloroquine product about 148g, yield of 87.2%, HPLC purity > 99.5%, maximum single impurity <0.1%.

[0041] Example 4 Synthesis of Hydroxychloroquine

[0042] In a 500 mL four-necked flask, 4,7-dichloroquinoline: 100 g (0.51 mol) and hydroxychloroquin side chain: 100 g (0.57 mol), heated to 110 ° C for 1 hour, and then heated to 130 ° C for 18 hours. The plate was monitored until 4,7-dichloroquinoline disappeared, cooled to room temperature, dissolved in isopropanol (1200 mL), 1.0 eq of sodium tert-butylate (48.96 g) was added in portions, stirred for 1-2 h, cooled, insoluble The precipitate was separated, and the insoluble material was filtered, and the filtrate was concentrated to dryness under reduced pressure, and then isopropyl acetate was used to be pulverized and filtered to obtain 167.8 g of crude hydroxychloroquine.

[0043] The above crude hydroxychloroquine was added to a mixed solvent of isopropyl alcohol-isopropyl acetate (1:7, v/v, 1200 mL), heated to 80 ° C to dissolve, and then naturally cooled to room temperature, stirred for 8 h, filtered, filtered. The cake was rinsed with a small amount of isopropyl acetate, and dried at 50 ° C to constant weight to obtain about 150 g, the yield was 88.3%, the HPLC purity was >99.5%, and the maximum single impurity was <0.1%.

[0044] Example 5 Synthesis of Hydroxychloroquine

[0045] In a 500 mL four-necked flask, 4,7-dichloroquinoline was added: 100 g (0.51 mol) and hydroxychloroquine side chain: 104 g (0.60 mol), and the temperature was raised to 110 ° C for 48 hours, and the spot plate was monitored for 4, 7-two. Chloroquinoline disappeared, cooled to room temperature, dissolved in ethanol (1500 mL), 1.0 eq of potassium methoxide was added in portions, stirred for 2 h, insoluble matter was precipitated, and insolubles were removed by filtration, and the filtrate was concentrated to dryness under reduced pressure, then isopropyl acetate was added. The ester was beaten and filtered to obtain 168.5 g of crude hydroxychloroquine.

[0046] The above crude hydroxychloroquine was added to a mixed solvent of isopropyl alcohol-isopropyl acetate (1:8, v/v, 1500 mL), heated to 80 ° C to dissolve, and then naturally cooled to room temperature, stirred for 5 h, filtered, filtered. The cake was rinsed with a small amount of isopropyl acetate, and dried at 50 ° C to constant weight to obtain about 145 g, the yield was 85.4%, the HPLC purity was >99.5%, and the maximum single impurity was <0.1%.

[0047] Example 6 Synthesis of Hydroxychloroquine Sulfate

[0048] 10.0 g of hydroxychloroquine product was added to a 250 mL four-necked flask, 100 mL of ethanol was added, and the mixture was stirred and dissolved at room temperature, and an equivalent amount of dilute sulfuric acid (2.97 g of concentrated sulfuric acid + 7 mL of water) was added dropwise to control the dropping rate, and the internal temperature of the reaction liquid was not higher than After 40 ° C, the mixture was stirred at room temperature for 18 hours, filtered, rinsed with 10 mL×2 ethanol, and dried at 50 ° C for 2 hours to obtain 12.2 g of white crystalline powder, HPLC purity >99.6%, maximum single impurity <0.1%.

[0049] Example 7 Preparation of Hydroxychloroquine Sulfate

[0050] Take 10.0g of hydroxychloroquine product into a 250mL four-necked flask, add 90mL of ethanol, stir to dissolve at room temperature, add equivalent amount of dilute sulfuric acid (2.97g concentrated sulfuric acid + 7mL water + 10mL ethanol), control the drop rate, the internal temperature of the reaction solution Not higher than 40 ° C, added, stirred at room temperature for 18 hours, filtered, rinsed with 10 mL × 2 ethanol, blasted at 50 ° C for 2 hours to obtain 12.0 g of white crystalline powder, HPLC purity > 99.6%, maximum single impurity <0.1 %.

[0051] Example 8 Synthesis of Hydroxychloroquine Sulfate

[0052] 10.0 g of hydroxychloroquine product was added to a 250 mL four-necked flask, 80 mL of ethanol was added, and the solution was dissolved at room temperature, and an equivalent amount of dilute sulfuric acid (2.97 g of concentrated sulfuric acid + 7 mL of water + 20 mL of ethanol) was added dropwise to control the drop rate and the internal temperature of the reaction solution. Not higher than 40 ° C, added, stirred at room temperature for 18 hours, filtered, rinsed with 10 mL × 2 ethanol, blasted at 50 ° C for 2 hours, to obtain 12.2 g of white crystalline powder, HPLC purity > 99.6%, maximum single impurity <0.1 %.

[0053] Example 9 Synthesis of Hydroxychloroquine Sulfate

[0054] 10.0 g of hydroxychloroquine product was added to a 250 mL four-necked flask, 70 mL of ethanol was added, and the mixture was stirred and dissolved at room temperature, and an equivalent amount of dilute sulfuric acid (2.97 g of concentrated sulfuric acid + 7 mL of water) was added dropwise to control the dropping rate, and the internal temperature of the reaction liquid was not higher than After addition at 40 ° C, the mixture was stirred at room temperature for 18 hours, filtered, rinsed with 10 mL of 2 ethanol, and dried at 50 ° C for 2 hours to obtain 12.3 g of white crystalline powder, HPLC purity >99.6%, maximum single impurity <0.1%.

[0055] Example 10 Synthesis of Hydroxychloroquine Sulfate

[0056] Take 10.0g of hydroxychloroquine product into a 250mL four-necked flask, add 60mL of ethanol, stir to dissolve at room temperature, add equivalent amount of dilute sulfuric acid (2.97g concentrated sulfuric acid + 7mL water + 40mL ethanol), control the drop rate, the reaction liquid internal temperature Not higher than 40 ° C, added, stirred at room temperature for 18 hours, filtered, rinsed with 10 mL × 2 ethanol, and dried by air at 50 ° C for 2 hours to obtain 12.1 g of white crystalline powder, HPLC purity > 99.6%, maximum single impurity < 0.1 %.

CN103472154
Method for analysis of hydroxychloroquine sulfate raw material and preparation by high performance liquid chromatography
[PDF]

Abstract
The invention belongs to the field of drug analysis and discloses a method for analysis of a hydroxychloroquine sulfate raw material and preparation by high performance liquid chromatography. The method can realize effective separation of related substances in hydroxychloroquine sulfate so that hydroxychloroquine sulfate quality is controlled, hydroxychloroquine sulfate raw material and preparation content is accurately determined, and hydroxychloroquine sulfate stability is indicated. The method has the advantages of strong specificity, high accuracy and simple operation.

The invention belongs to the field of drug analysis, and specifically relates to an analysis by high performance liquid chromatography Hydroxychloroquine sulfate raw materials and preparation methods.

Background technique

Hydroxychloroquine sulfate is used to treat discoid lupus erythematosus and systemic lupus erythematosus, and similar Rheumatoid arthritis and other drugs. Its structural formula is: The chemical name is 2-[[4-[(7-chloro-4-quinoline)amino]pentyl]ethylamino]-ethanolsulfur Acid salt. For the related substances introduced in the synthesis of synthetic hydroxychloroquine sulfate and degraded in storage, Whether it is in the bulk drug or the preparation, it needs to be controlled. Therefore, to achieve The separation of chloroquine and its related substances is used in the quality control of the synthesis and preparation of hydroxychloroquine sulfate The system has important practical significance.
At present, the national standards and ministerial standards of the People's Republic of China, BP (2012), USP （36）Among them, thin layer chromatography is used. After research, it is found that thin layer chromatography is used to detect The related substances of hydroxychloroquine sulfate have the problems of not strong specificity, low sensitivity, and thin Layer chromatography can only detect the limits of related substances, but cannot determine the exact amount of impurities. and In the content determination method of hydroxychloroquine sulfate and its preparations, chloroform is often used to extract hydroxychloroquine, Measured by non-aqueous titration method. Because chloroform is more toxic, it is easy to cause experimental operators Harm and easily pollute the environment.

Summary of the invention
The innovation of the present invention lies in the development of high performance liquid chromatography for the detection of hydroxychloroquine sulfate Related substances and content in raw materials and preparations, high performance liquid chromatography as a chromatographic analysis The method has the advantages of good separation effect, high sensitivity and fast analysis speed.
The invention overcomes the lack of specificity, low sensitivity and poor use of existing detection methods. Disadvantages of toxic agents. The chromatographic conditions are: Stationary phase: octadecyl silane bonded silica gel or octane silane bonded silica gel Mobile phase: mixed solvent composed of water-soluble organic solvent and buffer solution;

using isocratic Or gradient elution.
Flow rate: 0.5～2.0ml/min
Detection wavelength: 220～300nm
Among them, the salt for preparing the buffer solution includes acetate, phosphate, cation pair reagent, etc. Among them, phosphates are preferred, mainly selected from potassium dihydrogen phosphate, sodium dihydrogen phosphate, dipotassium hydrogen phosphate, Disodium phosphate. The mobile phase contains a certain amount of triethylamine, which helps reduce the main component chromatographic peaks The amount of triethylamine is 0.01%～1%V/V of the buffer solution, and the mobile phase is slow The pH selection range of the rinse is 7.2-8.2, preferably pH 8.0.
Wherein, the water-soluble organic solvent in the mixed solvent of the mobile phase is: methanol or ethyl Nitrile, or other water-soluble organic solvents acceptable for liquid chromatography.
In the quality control method of the present invention, the wavelength 220～ 270nm; When performing content determination, a wavelength of 245-300 nm can be selected; among them, 254 nm is preferred.
This method overcomes the lack of specificity, sensitivity and use of existing detection methods. Disadvantages of toxic agents.
Figure 1 shows that the impurities 1, 2, and 3 in the raw material of hydroxychloroquine sulfate are hydroxyquinoline, LC45-1, dichloroquinoline (retention times are 7.833, 13.547, 24.820min), It is well separated from the peak of hydroxychloroquine sulfate (retention time 20.447min).
Description of the drawings
Figure 1: Related substances detected in specific embodiment 1 of the present invention Product related substance detection map. Impurities 1, 2, 3 are hydroxyquinoline, LC45-1, two Chloroquinoline (retention time is 7.833, 13.547, 24.820min), hydroxychloroquine sulfate Peak (retention time 20.447min)
Figure 2: A comparative map of related substances detected in specific embodiment 1 of related substances of the present invention, Related substance control solution map. Hydroxychloroquine sulfate peak (retention time 20.573min)
Figure 3: The chromatogram of the test solution in the content specific example 1 of the present invention, the content is measured Set, the chromatogram of the test solution. Hydroxychloroquine sulfate peak (retention time 20.084min)
Figure 4: The chromatogram of the reference substance solution in the content specific example 1 of the present invention, and the content is measured In the calibration, the chromatogram of the reference solution: hydroxychloroquine sulfate peak (retention time 20.103min)
detailed description
The present invention will be further described in detail below through specific embodiments, but it should not be understood In order to limit the scope of protection of the present invention, based on the above-mentioned technical ideas, common use in the field Modifications, replacements, and alterations made by common technical knowledge and conventional means fall within the scope of the present invention.
Specific Example 1: Detection of Related Substances:
Use octyl silane-bonded silica gel as filler, and use phosphoric acid buffer solution (take dihydrogen phosphate Potassium 2.72g, put in 1000ml water, add 2ml triethylamine, adjust with 1mol potassium hydroxide pH to 8.0±0.05 is mobile phase A, methanol is mobile phase B, and gradient elution is performed according to the following table:
The detection wavelength is 254nm.
The number of theoretical plates should not be lower than the peak of hydroxychloroquine

sulfate 2000。
Take an appropriate amount of hydroxychloroquine sulfate raw material and add a solvent [mobile phase A-methanol (53:47)] to dissolve it Dissolve and dilute to make a solution containing 0.5mg per 1ml as the test solution; take an appropriate amount accurately The amount, diluted with the above solvent to make a solution containing 5μg per 1ml as a control solution. respectively Precisely measure 20μl each of the test solution and the control solution, inject into the liquid chromatograph, and record the color Spectrogram. Calculate the content of related substances according to its own low concentration control method.
Specific Example 2: Detection of Related Substances:
Use octyl silane-bonded silica gel as filler, and use phosphoric acid buffer solution (take dihydrogen phosphate Sodium 3.12g, put in 1000ml water, add 5ml triethylamine, adjust with 1mol potassium hydroxide pH to 8.0±0.05) is mobile phase A, acetonitrile is mobile phase B, and gradient elution is performed according to the following table:
The detection wavelength is 254nm.
The number of theoretical plates should not be lower than the peak of hydroxychloroquine sulfate
2000。
Take an appropriate amount of hydroxychloroquine sulfate raw material and add a solvent [mobile phase A-acetonitrile (60:40)] to dissolve it Dissolve and dilute to make a solution containing 0.5mg per 1ml as the test solution; take an appropriate amount accurately The amount, diluted with the above solvent to make a solution containing 5μg per 1ml as a control solution. respectively Precisely measure 20μl each of the test solution and the control solution, inject into the liquid chromatograph, and record the color Spectrogram. Calculate the content of related substances according to its own low concentration control method.
Specific Example 3: Detection of Related Substances:
Use octadecyl silane-bonded silica gel as a filler, and use a phosphoric acid buffer solution 5.44g potassium hydrogen, put in 1000ml water, add 3ml triethylamine, dissolve it with 1mol/L potassium hydroxide Adjust the pH to 8.0±0.05)-methanol (60:40) as the mobile phase, the detection wavelength is 254 nm. The number of theoretical plates should not be less than 2000 based on the peak of hydroxychloroquine sulfate.
Take an appropriate amount of hydroxychloroquine sulfate raw material, dissolve and dilute it with mobile phase to make it contain per 1ml 0.4mg solution is used as the test solution; accurately measure an appropriate amount, dilute with mobile phase to make
A solution containing 4μg in ml was used as a control solution. Precisely take the test solution and control separately 20μl each of the solution was injected into the liquid chromatograph, and the chromatogram was recorded. According to its own low concentration control method Calculate the content of related substances.
Specific Example 4: Detection of Related Substances:
Use octadecyl silane-bonded silica gel as a filler, and use a phosphoric acid buffer solution 5.44g potassium hydrogen, put in 1000ml water, add 2ml triethylamine, and dissolve it with 1mol/L potassium hydroxide Adjust the pH to 8.0±0.05)-methanol (60:40) as the mobile phase, the detection wavelength is 254 nm. The number of theoretical plates should not be less than 2000 based on the peak of hydroxychloroquine sulfate.
Take an appropriate amount of hydroxychloroquine sulfate raw material, dissolve and dilute it with mobile phase to make it contain per 1ml 0.4mg solution is used as the test solution; accurately measure an appropriate amount, dilute with mobile phase to make 1 A solution containing 4μg in ml was used as a control solution. Precisely take the test solution and control separately 20μl each of the solution was injected into the liquid chromatograph, and the chromatogram was recorded. According to its own low concentration control method Calculate the content of related substances.

Specific Example 5 for Detection of Related Substances:
Use octadecyl silane-bonded silica gel as a filler, and use a phosphoric acid buffer solution 5.44g potassium hydrogen, put in 1000ml water, add 1ml triethylamine, and dissolve it with 1mol/L potassium hydroxide Adjust the pH to 8.0±0.05)-methanol (60:40) as the mobile phase, the detection wavelength is 254 nm. The number of theoretical plates should not be less than 2000 based on the peak of hydroxychloroquine sulfate.
Take an appropriate amount of hydroxychloroquine sulfate tablet powder, dissolve it with mobile phase and dilute it to make the content per 1ml 0.4mg of the solution, filter, take the continued filtrate as the test solution; accurately measure an appropriate amount, use The mobile phase was diluted to make a solution containing 4μg per 1ml as a control solution. Respectively accurately measure 20μl each of the test solution and the control solution were injected into the liquid chromatograph, and the chromatogram was recorded. press Calculate the content of related substances by its own low concentration control method.
Specific Example of Assay 1:
Use octyl silane-bonded silica gel as filler, and use phosphoric acid buffer solution (take dihydrogen phosphate Potassium 2.72g, put in 1000ml water, add 2ml triethylamine, adjust with 1mol potassium hydroxide (pH to 8.0±0.05) is mobile phase A, methanol is mobile phase B, perform gradient washing according to the following table Off:
The detection wavelength is 254nm.
The number of theoretical plates should not be lower than the peak of hydroxychloroquine sulfate 2000。
Take an appropriate amount of hydroxychloroquine sulfate raw material, accurately weigh it, and add solvent [mobile phase-A methanol (53：47)] Dissolve and dilute quantitatively to make a solution containing 0.1mg per 1ml as a test Product solution; another appropriate amount of hydroxychloroquine acid reference substance dried at 105°C, accurately weighed, plus The solvent is dissolved and diluted to prepare a solution containing approximately 0.1 mg per 1 ml as a reference solution; Measure 20μl of the above test solution and reference solution and inject into the liquid chromatograph, record Chromatogram. Calculate the peak area according to the external standard method to obtain.
Specific example of content determination 2:
Use octadecyl silane-bonded silica gel as a filler, and use a phosphoric acid buffer solution 2.72g potassium hydride, put in 1000ml water, add 2ml triethylamine, adjust with 1mol potassium hydroxide PH to 8.0±0.05)-methanol (60:40) is the mobile phase, and the detection wavelength is 329nm. The number of theoretical plates should not be less than 2000 based on the peak of hydroxychloroquine sulfate.
Take an appropriate amount of hydroxychloroquine sulfate raw material, accurately weigh it, add mobile phase to dissolve and dilute quantitatively Make a solution containing 0.1mg per 1ml as the test solution; take another after drying at 105℃ An appropriate amount of hydroxychloroquine acid reference substance, accurately weighed, dissolved in mobile phase and diluted to make each 1ml The solution containing about 0.1mg in the medium is used as the reference solution; respectively measure the above-mentioned test solution and the Inject 20μl of the product solution into the liquid chromatograph and record the chromatogram. Calculate by peak area according to external standard method Count, get it.
Specific example of content determination 3:
Use octyl silane-bonded silica gel as filler, and use phosphoric acid buffer solution (take hydrogen phosphate dibasic Sodium 4.0g, put in 1000ml water, add 2ml triethylamine, adjust with 1mol potassium hydroxide (pH to 8.0±0.05)-acetonitrile (70:30) is the mobile phase, and the detection wavelength is 254nm. The number of theoretical plates should not be less than 2000 based on the peak of hydroxychloroquine sulfate.
Take 20 hydroxychloroquine sulfate tablets, accurately weigh, grind finely, take an

appropriate amount of fine powder, and add flow Dissolve the phases and dilute quantitatively to make a solution containing 0.1mg per 1ml, filter, and take the subsequent filtrate as It is the test solution; another appropriate amount of hydroxychloroquine acid reference substance dried at 105°C, accurately weighed, Add mobile phase to dissolve and dilute to make a solution containing about 0.1mg per 1ml as a reference solution Solution; respectively measure 20μl of the above-mentioned test solution and reference solution and inject into the liquid chromatograph, Record the chromatogram. Calculate the peak area according to the external standard method to obtain.

KR101115412
NEW PREPARATION OF HYDROXYCHLOROQUINE
[PDF]

PURPOSE: A method for preparing hydroxychloroquine is provided to suppress generation of by-product by reducing reaction temperature and time and prepare the hydroxychloroquine with high yield and purity. CONSTITUTION: A hydroxychloroquine of chemical formula 1 is prepared by reacting... step of reacting sulfuric acid with hydroxychloroquine to obtain hydroxychloroquine sulfate.

The present invention relates to a method for producing hydroxychloroquine which is a therapeutic agent for malaria.

Hydroxychloroquine has the structure of the following formula 1 and its chemical name is 2 - [[4- [7-chloro-4-quinolinyl] amino] pentyl] 4- [7-chloro-4-quinolinyl] amino] pentyl] - ethylamino] ethanol} was first disclosed in U.S. Patent No. 2,546,658. N'-N'-hydroxyethyl-1,4-pentanediamine {N'ethyl-N ', N'-tetramethyluronium hexafluorophosphate) β-hydroxyethyl-1,4-pentadiamine} was reacted with potassium iodide (KI) and a phenol solvent at 125-130 ° C. for 18 hours or longer to prepare crude hydroxychloroquine, (S) -N'ethyl-N '[beta] -hydro-quinoline in the case of U.S. Pat. No. 5,314,894, (S) - (+) - hydroxycroquinoline {(R) - (R) -methyl-2- S) - (+) - hydroxychloroquine}. In Canadian patent CA 2,561,987, 4,7-dichloroquinoline (2) and N'ethyl- After reacting cyethyl-1,4-pentadiyimine (3) at 120-130 ° C for 20-24 hours, a protecting group is introduced into the reaction product as follows to easily remove the impurities, and then the protecting group is hydrolyzed (PG in formula (A), (B) and (C) means a protecting group). However, the known processes for preparing hydroxychloroquine and its acid addition salt include a method of producing toxic phenol Use of the same solvent or a reagent such as N, N-diisopropylethylamine having a high boiling point and a similar form to the final product makes it difficult to remove by-products during the production of the acid salt. Moreover, since the long reaction time at high temperature increases the production cost and increases the production of by-products, there is a demand for a method of synthesizing hydroxychloroquine and dicellulose salt, which is more efficient in the industrial field. It is necessary to develop new synthesis method of hydroxychloroquine which overcomes various disadvantages and shows high purity and yield.

An object of the present invention is to provide a novel process for the production of hydroxychloroquine which suppresses the production of by-products and reduces the production cost by significantly lowering the reaction temperature and the reaction time by using a pressure without using a catalyst and a reaction solvent The present invention relates

to a novel process for the preparation of hydroxychloroquine using pressure, which comprises reacting 4,7-dichloroquinoline and N'-ethyl-N '? -Hydroxyethyl-1,4-pentanediamine at high pressure The process of the present invention can be carried out by reacting 4,7-dichloroquinoline with N, N'-ethyl-N'-tetrachloroquinoline without using a catalyst and a solvent, In the present invention, the high pressure means a pressure exceeding 1 atm (about 1 bar) higher than the atmospheric pressure, and a pressure of 5 bar to 30 b The high pressure in the present invention is due to inert gas such as nitrogen gas or argon gas or air without moisture. In the present invention, the reaction time is preferably 10 to 20 bar, The reaction temperature may be varied within a range of 80 to 150 ° C. and more preferably 100 to 120 ° C. In the present invention, 4, The reaction molar ratio of 7-dichloroquinoline and N'-ethyl-N '? -Hydroxyethyl-1,4-pentadiamine can be varied, but is preferably 1: 1.05 to 1.5, more preferably 1: 1.05-1.1 The present invention also provides a process for preparing hydroxy chloroquinone represented by the following formula (1): (a) reacting 4,7-dichloroquinoline with N'ethyl-N '? -Hydroxyethyl-1,4- And (b) reacting the hydroxides prepared in step (a) The present invention also provides a process for preparing hydroxychloroquine sulfate comprising reacting chloroquine with sulfuric acid (H2SO4) to prepare hydroxychloroquine sulfate. The reaction conditions of step (a) are as described above. The method for preparing hydroxychloroquine according to the present invention is characterized in that 4,7-dichloroquinoline and N'-ethyl-N '? -Hydroxyethyl-1,4-pentanediamine are reacted with 1 : 1.1 molar ratio, put into a high-pressure reactor and pressurize with nitrogen pressure from 5 bar to 20 bar, preferably from 10 bar to 15 bar. The mixture is stirred at 80 ° C for 30 minutes until the 4,7-dichloroquinoline is dissolved, and then stirred at 100 ° C to 120 ° C for 4 hours to 6 hours. , The reaction temperature and the reaction time are remarkably lowered to inhibit the production of by-products, and hydroxychloroquine is produced at a high purity and a high yield, and the production cost is reduced.

Hereinafter, preferred embodiments of the present invention will be described in order to facilitate understanding of the present invention. However, the following examples are provided only for the purpose of easier understanding of the present invention, and the contents of the present invention are not limited by the examples. Example 1 Preparation of Hydroxychloroquine Using 20 Bar Pressure 10 Kg of 4,7-dichloroquinoline and 10 g of N'-ethyl-N '? - hydroxy 11.4 Kg (1.0 eq) of ethyl-1,4-pentadiamine was charged into a high-pressure reactor and charged with 20 bar of nitrogen gas. The mixture was stirred at 80 ° C for 30 minutes and then at 100 ° C to 110 ° C for 4 hours. 30Kg of 3N HCl aqueous solution and 20Kg of chloroform were added thereto. The mixture was cooled to room temperature and stirred for 1 hour. After the mixture was allowed to stand, the resulting product was transferred to an aqueous layer and the remaining by-products to a chloroform layer. This procedure was repeated three times and an aqueous layer with the desired compound was collected. The collected water layer was extracted with 40Kg of 2N NaOH and chloroform solvent, and the aqueous layer was removed. 5Kg of activated carbon and 5Kg of alumina were added, and the mixture was stirred at 40 ° C for 6 hours and then filtered. The filtrate was concentrated under reduced pressure and 60 Kg of ethylene glycol (EDC) was added thereto to crystallize the crystals. After filtration and vacuum drying at 40 DEG C, 14 Kg (yield 78.2%) of the title compound was obtained. 1H NMR (500 MHz) (d), 7.32 (d), 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) Example 2 Preparation of Hydroxychloroquine (Formula 1) Using 10 bar Pressure 10 kg of 4,7-dichloroquinoline and N'- -1,4-pentadiamine (11 eq.) Was charged into a high-pressure reactor and charged with nitrogen gas at 10 bar. The mixture was stirred at 80 ° C for 30 minutes and then at 100 ° C to 110 ° C for 6 hours. 30Kg of 3N HCl aqueous solution and 20Kg of chloroform were added thereto. The mixture was cooled to room temperature, stirred

and allowed to stand, and the resulting product was transferred to an aqueous layer and the remaining by-products to a chloroform layer. This procedure was repeated three times and an aqueous layer with the desired compound was collected. The collected water layer was extracted with 40 Kg aqueous solution of 2N NaOH and 20 Kg of chloroform solvent to remove the aqueous layer. 5 Kg of activated carbon and 5 Kg of alumina were added and stirred at 40 ° C for 6 hours and filtered. The filtrate was concentrated under reduced pressure, 60 Kg of EDC was added to crystallize, followed by filtration and vacuum drying at 40 DEG C to obtain 14.5 g (yield 75.5%) of the title compound. 1H NMR (500 MHz) Example 3 Preparation of Hydroxychloroquine Sulfate 10 Kg of hydroxychloroquine prepared in Example 1 was dissolved in 100 Kg of ethanol and then cooled to 10 ° C. To this solution was added 1.58 Kg of concentrated sulfuric acid (1.0 eq) dissolved in 50 kg of ethanol was stirred for 12 hours while slowly adding thereto. (D2) 8.08 (d), 7.95 (d), 7.53 (d), 7.35 (dd), 6.64 (d, 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) Example 4 Preparation of Hydroxychloroquine Sulfate 10 Kg of the hydroxychloroquine prepared in Example 1 was dissolved in 100 Kg of ethyl acetate, and a solution prepared by dissolving 1.58 Kg (1.0 eq) of concentrated sulfuric acid in 50 Kg of ethyl acetate was added to the solution at 30 ° C while stirring slowly. After stirring for 12 hours at 0 ° C, 10.0 Kg (77.5%) of the title compound was obtained by filtration.

CN102050781A
Industrial preparation method of hydroxychloroquine sulfate
[PDF]

Abstract
The invention relates to an industrial preparation method of hydroxychloroquine sulfate, which comprises heating 4, 7-dichloroquinoline and hydroxychloroquine side chain at refluxing temperature to 120-125 DEG C, allowing reaction to obtain hydroxychloroquine, and reacting with sulfuric acid to obtain hydroxychloroquine sulfate. The method can obtain high-purity hydroxychloroquine sulfate with single impurity less than or equal to 0.1% and purity higher than or equal to 99.5%; and has less preparation procedures, simple process, high product yield, good quality, low environmental pollution, no use of highly toxic solvent, and is easy for industrial production.

[0001] Technical field

[0002] The invention belongs to the field of chemistry or medicinal chemistry, and particularly relates to an industrial preparation method of hydroxychloroquine sulfate. The side chain of 4,7-dichloroquinoline and hydroxychloroquine is heated at a reflux temperature and slowly heated to 120 ° C-125 ° C The hydroxychloroquine is prepared, and then reacted with sulfuric acid to obtain hydroxychloroquine sulfate. This method can obtain high purity hydroxychloroquine sulfate with single impurity ≤0.1% and purity ≥99.5%.

[0003] Background technique

[0004] The structure of hydroxychloroquine sulfate is shown below. Its chemical name is 2-[[4-[(7-chloro-4-quinolinyl) amino] pentyl] ethylamino] -ethanol sulfate, CAS number is 747-36- 4. Hydroxychloroquine sulfate was successfully developed by Winthrop Corporation. It was first listed in the United States in 1956 and has been listed in many countries and regions

such as France, Denmark, Japan, Germany, and Finland. The US FDA approved hydroxychloroquine sulfate tablets for the treatment of lupus erythematosus and rheumatoid arthritis on May 29, 1998.

[0005]

[0006] CA2561987 discloses a method for preparing hydroxychloroquine, the method is as follows,

[0007]

[0008] The method includes sequentially adding isopropyl alcohol (2vol), 4-amino-N-ethyl-(2-hydroxyethyl) -pentylamine (1.5eq, 0.75mol), 4,7-dichloroquinoline (1.0eq, 0.5mol), stir, heat, stir at 120-130 ℃ for 20-24h, then cool to 70-80 ℃, add water (2vol) and methyl isobutyl ketone (3vol), adjust the pH at 10-11, min Liquid, add acetic anhydride (0.1eq) to the organic layer, stir at room temperature overnight, then add LiOH-H2O (0.25eq), water (0.5vol) and methanol (0.5vol) in sequence, the mixture was stirred at room temperature overnight, Wash again with water. Add methanol (5vol) and sulfuric acid (1.0eq, 0.5mol) to the organic layer, heat to 35-45 ° C and stir for 3-4h, then cool to 20-25 ° C, filter, and wash the filter cake with methanol to obtain hydroxychloroquine sulfate Crude product, yield 80%, chromatographic purity greater than 99.5%. The impurity 7-chloro-4- (4-N-hydroxyethyl-1-methyl tertiary amino) quinoline is less than 0.1%. Add the crude product obtained above (200.0g), water (1L) and methyl isobutyl ketone (800ml), stir to dissolve, cool to 0-5 ℃, add 5N sodium hydroxide until the pH is 10.5-11.0, Stir at room temperature for 0.5-1h, separate the liquid, add 5% sodium chloride solution (200ml) to the organic layer and wash with activated carbon (20.0g), stir at room temperature, filter, wash the filter cake with methanol (200ml), spin-dry the filtrate, Get hydroxychloroquine. The purification process of hydroxychloroquine and its sulfate in this method is very complicated, especially in the post-treatment to remove ethyl impurities (7-chloro-4- (4-N-hydroxyethyl-1-methyl tertiary amino) After a complicated post-processing process, the impurities are finally controlled to less than 0.1%, which has high cost and long time, which is not conducive to industrial production.

[0009] US2546658 (equivalent to GB680255, DE838142) discloses a synthesis method of hydroxychloroquine. The reaction process of this method is as follows:

[0010]

[0011] The operation of this method is as follows: 4,7-dichloroquinoline (90g), phenol (90g), potassium iodide (1.0g), 5- (N-ethyl-N-2-hydroxyethylamino) -2 -Pentylamine (132g), stirred, heated, stirred at 125-130 ° C for 18h, after which the reaction solution was cooled, methanol (1.9L) was added, the reaction solution was filtered with charcoal, and the clear filtrate was added to methanol (300ml) Phosphoric acid (100g), wipe the wall with a glass rod and let it stand for 2 days, suction filtration, washing the filter cake with methanol and drying to obtain hydroxychloroquine diphosphate (10lg), yield 41.9%, melting point 155-156 ° C. The obtained phosphate was dissolved in water, completely dissociated with ammonium hydroxide, extracted with chloroform, distilled off chloroform, and the residue was recrystallized with ether to obtain crude hydroxychloroquine (30g), melting point 77-82 ° C, yield 44.3%. Dichloromethane and ethyl acetate can be further added to recrystallize to obtain pure hydroxychloroquine, melting point 89-91 ° C.

[0012] The method of US2546658 uses phenol with a weight ratio of 1: 1 as the reaction catalyst. Phenol is toxic and corrosive. Its concentrated solution is strongly corrosive to the skin. After treatment, it is converted into sodium phenol wastewater. Phenol-containing wastewater is one of the most harmful and difficult to treat in industrial wastewater. It is one of the wastewaters that are currently controlled in China. It has a large environmental pollution; phenol has a melting point of 42 ° C and is solid at room temperature. To successfully feed, it must be heated to dissolve into a liquid In order to feed, the operation is very cumbersome, and industrial production is difficult; the reaction does not involve the solvent, the material is very viscous, and the selectivity of mass transfer, heat transfer, transmission, and reaction is very poor. It is necessary to remove impurities by forming phosphate, 4, 7-two The yield of chloroquinoline to crude hydroxychloroquine is 44.3%, the production cost is high, and it is difficult to implement industrial production. At the same time, this method is not suitable for industrial production.

[0013] WO2010027150 also discloses a method for synthesizing hydroxychloroquine sulfate, whose reaction circuit is as follows:

[0014]

[0015] The method includes sequentially adding 4,7-dichloroquinoline, 4-amino-N-ethyl- (2-hydroxyethyl) -pentylamine, pressurizing with nitrogen or argon to maintain the pressure at 5-20bar Stir at 30 ° C for 30min, warm to 100-120 ° C and react for 4-6h. After the reaction is complete, add dilute hydrochloric acid and chloroform to acidify hydroxychloroquine. At this time, hydroxychloroquine forms a hydrochloride and dissolves in the aqueous phase. After collecting the aqueous phase, add sodium hydroxide to alkalinize and extract hydroxychloroquine with chloroform. The chloroform layer is concentrated and dichloromethane is used after concentration. The hydroxychloroquine product is obtained after crystallization of ethane. Hydroxychloroquine is added with sulfuric acid under the condition of ethanol as a solvent to obtain hydroxychloroquine sulfate.

[0016] The method of **WO2010027150** still has the following disadvantages:

[0017] 1、Promote the condensation reaction by pressurizing in the autoclave, but because the pressure range is 5-20 bar, it has great safety risks in industrial applications;

[0018] 2、The post-treatment of the reaction is to obtain hydroxychloroquine product by recrystallization after acidification and alkalization, which is equivalent to two refinings, and the product yield is greatly lost. At the same time, chloroform and dichloroethane are selected for extraction and recrystallization, which are both toxic Very large reagents should be avoided in the production of APIs.

[0019] According to the three methods disclosed above, the method of CA2561987 has certain advantages in environmental protection and reaction conditions compared to other methods. No toxic reagents and high pressure are used. However, the reaction time is maintained at 120-130 ° C for up to 20 -24h, it will cause the impurity content in the crude product to be too high, increasing the post-treatment pressure, and also has the following prominent shortcomings:

[0020] 1、The control of the reaction also needs to be refined. If the temperature rise process of the reaction is strictly controlled, the content of by-products in the crude product will be

further reduced, and at the same time, the conversion rate of the product will be improved and the production cost will be reduced.

[0021] 2、5-(N-ethyl-N-2-hydroxyethylamino) -2-pentylamine (referred to as "hydroxychloroquine side chain" in the present invention) is used in a large amount, and the amount of hydroxychloroquine side chain is 4,7-di The 2-3 times of chloroquinoline makes the hydroxychloroquine side chain account for a large proportion of the cost, resulting in too high production costs.

[0022] 3、In order to remove 7-chloro-4- (4-N-hydroxyethyl-1-methyl tertiary amino) quinoline during the post-treatment of the reaction, a more expensive methyl isobutyl ketone was used, and the steps were complicated , Increasing production costs.

[0023] 4、There are many overnight treatment operations in post-processing, and there will be uncertainty in the operation time when applied to production, resulting in production deviations.

[0024] In general, the current methods of synthesizing hydroxychloroquine sulfate use highly toxic catalysts and solvents, the synthesis route is lengthy, the reaction selectivity is poor, the reaction period is long, special pressure-resistant equipment is required, the post-reaction treatment is cumbersome and difficult to operate, and the production cost is high , Insufficient product content, etc. Therefore, it is necessary to further improve the method for preparing hydroxychloroquine sulfate in order to obtain a more efficient, simpler, more selective, more environmentally friendly, and lower cost method for preparing high-purity hydroxychloroquine sulfate.

[0025] Summary of the invention

[0026] The purpose of the present invention is to provide an industrial preparation method for hydroxychloroquine sulfate. This method can increase the purity of hydroxychloroquine in the reaction solution by controlling the temperature and time of distilling off the solvent by gradually raising the temperature during the reaction process and the reaction time. With regard to the content of related impurities, hydroxychloroquine sulfate with higher yield and high purity is obtained, with a purity ≥ 99.7% and a single impurity ≤ 0.1%. The method also avoids the use of toxic solvents and catalysts, which is beneficial to environmental protection. The reaction conditions are mild, high pressure is avoided, the amount of hydroxychloroquine side chains is reduced, the post-processing is simple, and the production cost is significantly reduced. Therefore, it is particularly suitable for industrial production.

[0027] To achieve the purpose of the present invention, the following embodiments are provided:

[0028] In one embodiment, an industrial preparation method of hydroxychloroquine sulfate of the present invention includes:

[0029] Condensation reaction of 4,7-dichloroquinoline and hydroxychloroquine side chain in an organic solvent by heating and gradually distilling off the solvent to obtain crude hydroxychloroquine, which is recrystallized to obtain hydroxychloroquine, which is then converted into sulfuric acid Salt reaction to produce hydroxychloroquine sulfate,

[0030]

[0031] The method is characterized in that: the method of gradually raising the temperature to distill off the solvent includes: after heating the reaction solution to the initial reflux temperature, then distilling off the solvent by gradually raising the temperature for 7-12 hours to 120-125 ° C, preferably 9-10 hours, and then maintaining The reaction temperature is 120 ° C to 125 ° C for 13 to 18 hours, preferably 14 to 16 hours.

[0032] In the above embodiment, the organic solvent is selected from propanol, isopropanol, n-butanol and their mixed solvents, preferably isopropanol.

[0033] In the above scheme, the molar ratio of 4,7-dichloroquinoline to hydroxychloroquine side chain is 1: 1.2.

[0034] In the above embodiment, the recrystallization is performed in an organic solvent selected from the group consisting of ethanol, isopropanol, ethyl acetate, and mixed solvents thereof, preferably ethyl acetate and isopropanol.

[0035] In the above embodiment, the hydroxychloroquine reacts with concentrated sulfuric acid to form a salt, wherein the weight ratio of hydroxychloroquine to concentrated sulfuric acid is 1: 0.25 to 0.30.

[0036] In the above embodiment, the hydroxychloroquine reacts with concentrated sulfuric acid to form a salt, and the appropriate solvent is selected from ethanol, isopropanol, ethyl acetate and their mixed solvents, preferably ethyl acetate and ethanol.

[0037] In the above embodiment, after the reaction of 4,7-dichloroquinoline and hydroxychloroquine side chain is completed, the reaction product is extracted with dichloromethane, and the extract is distilled by heating to remove the dichloromethane to obtain crude hydroxychloroquine.

[0038] The term "hydroxychloroquine side chain" refers to the starting material "5- (N-ethyl-N-2-hydroxyethylamino) -2-pentylamine".

[0039] In the industrial preparation method of hydroxychloroquine sulfate of the present invention, in optimizing the preparation process of hydroxychloroquine sulfate, the inventors were surprised to find that the temperature in the reaction mixture of 4,7-dichloroquinoline and hydroxychloroquine side chain was controlled by stage heating The temperature and time for the organic solvent to evaporate, that is, during the evaporation of the organic solvent, it takes 7-12 hours to gradually increase the temperature from the temperature at the beginning of the reflux to 120-125 ℃, and the reaction under the conditions of 120 ℃ ~ 125 ℃ The time is shortened to 13-18 hours. At the same time, the lower molar ratio of 4,7-dichloroquinoline and hydroxychloroquine side chain can achieve the best balance between cost and yield, thereby reducing the amount of hydroxychloroquine side chain. The hydroxychloroquine with purity ≥ 99.5% can be obtained only by recrystallization during treatment. The purity of hydroxychloroquine sulfate after salt formation can reach 99.7% or more (determined by HPLC external standard method), and its single impurity ≤ 0.1%.

[0040] The industrial preparation method of hydroxychloroquine sulfate of the invention has few preparation steps, simple process, high product purity, ideal yield, mild reaction

conditions (no pressurized conditions), and avoids the use of corrosive reagents, which is less harmful to the environment and more suitable For industrial production.

[0041] Through the follow-up monitoring of the reaction state, we found that the condensation reaction is the main temperature range for the production of by-products at 125-130 ° C. If the reaction time is too long within this temperature range, the by-products of the product will increase, resulting in an increase in the content of impurities The inventors found that the conversion of raw materials and the control of impurities achieved the best balance by exploring the reaction temperature and time, and found that by controlling the heating method of the temperature-increasing reaction, first, by extending the temperature-rising reaction time below 120 ° C, the reaction was promoted as much as possible The conversion at this temperature improves the conversion rate of the raw material 4,7-dichloroquinoline; then the reaction time is reduced to 120-125 ° C and the reaction time is shortened to 13-18 hours in order to minimize side reactions at this high temperature Production, reduce the impurity content in the product. Due to the greatly reduced content of impurities, there is no need to use methyl isobutyl ketone, only one-step recrystallization using low-cost common solvents to obtain high-purity hydroxychloroquine products, its purity can reach more than 99.5%, while a single impurity ≤0.1%. By using this purity hydroxychloroquine to form a salt, hydroxychloroquine sulfate with a purity greater than 99.7% and a single impurity ≤0.1% can be obtained.

[0042] In short, the beneficial effects of the present invention are as follows: The present invention discloses a method for preparing hydroxychloroquine sulfate, using 4,7-dichloroquinoline as the starting material, and hydroxychloroquine sulfate is prepared by condensation and salt formation in two steps; The condensation reaction uses propanol, isopropanol, one or more of n-butanol as a solvent, and gradually increases the conversion rate and yield of the reaction by means of stage heating. For the crude product of hydroxychloroquine, ethanol, isopropanol, and ethyl acetate are used Recrystallization of esters or their mixed solvents improves the purity of hydroxychloroquine and keeps its purity above 99.5%; selecting a suitable solvent as a solvent in the salt formation reaction can further purify the product, improve product yield and quality, and reduce The production cost makes the purity of hydroxychloroquine sulfate HPLC external standard method above 99.7%, and the single impurity below 0.1%.

[0043] The method of the present invention does not use highly toxic reagents, the reaction and post-treatment processes are simple and controllable, no special pressure equipment is used, the environmental pollution is small, and it is very suitable for industrial production.

[0044] detailed description

[0045] The following examples are used to further explain the present invention, but do not limit the scope of the present invention.

[0046] Example 1. Preparation of hydroxychloroquine sulfate

[0047] a. Preparation of hydroxychloroquine

[0048] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely

dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ° C over 7 hours, and then kept at 120 ° C-125 ° C for 16 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 99.5%, maximum single impurity 0.12%, yield 58%;

[0049] b. Preparation of hydroxychloroquine sulfate

[0050] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 99.6%, the largest single impurity is below 0.1%, and the yield is 92%.

[0051] There are two steps from the starting material to the final product, and the total yield is 53.36%.

[0052] Example 2. Preparation of hydroxychloroquine sulfate

[0053] a. Preparation of hydroxychloroquine

[0054] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ° C over 10 hours, and then kept at 120 ° C-125 ° C for 16 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 99.8%, maximum single impurity 0.05%, yield 70%;

[0055] b. Preparation of hydroxychloroquine sulfate

[0056] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 99.85%, the largest single impurity is below 0.1%, and the yield is 92%.

[0057] There are two steps from the starting material to the final product, and the total yield is 64.4%.

[0058] Example 3. Preparation of hydroxychloroquine sulfate

[0059] a. Preparation of hydroxychloroquine

[0060] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ° C over 12 hours, and then kept at 120 ° C to 125 ° C for 16 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 99.5%, maximum single impurity 0.08%, yield 65%;

[0061] b. Preparation of hydroxychloroquine sulfate

[0062] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 99.7%, the largest single impurity is below 0.1%, and the yield is 92%.

[0063] There are two steps from the starting material to the final product, and the total yield is 59.8%.

[0064] Example 4. Preparation of hydroxychloroquine sulfate

[0065] a. Preparation of hydroxychloroquine

[0066] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ° C over 10 hours, and then kept at 120 ° C-125 ° C for 13 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 99.6%, maximum single impurity 0.11%, yield 55%;

[0067] b. Preparation of hydroxychloroquine sulfate

[0068] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is

washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 99.7%, the largest single impurity is 0.087%, and the yield is 92%.

[0069] There are 2 steps from the starting material to the final product, and the total yield is 50.6%.

[0070] Example 5. Preparation of hydroxychloroquine sulfate

[0071] a. Preparation of hydroxychloroquine

[0072] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ° C over 10 hours, and then maintained at 120 ° C-125 ° C for 18 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 98.7%, maximum single impurity 0.13%, yield 60%;

[0073] b. Preparation of hydroxychloroquine sulfate

[0074] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed

by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 99.4%, the largest single impurity is 0.1%, and the yield is 92%.

[0075] There are 2 steps from the starting material to the final product, and the total yield is 55.2%.

[0076] Comparative Example 1. Preparation of hydroxychloroquine sulfate

[0077] a. Preparation of hydroxychloroquine

[0078] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ° C over 6 hours, and then kept at 120 ° C-125 ° C for 12 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 99.3%, maximum single impurity 0.23%, yield 45%;

[0079] b. Preparation of hydroxychloroquine sulfate

[0080] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 99.5%, the largest single impurity is 0.20%, and the yield is 92%.

[0081] There are two steps from the starting material to the final product, and the total yield is 41.4%.

[0082] Comparative Example 2. Preparation of hydroxychloroquine sulfate

[0083] a. Preparation of hydroxychloroquine

[0084] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine 153g; in a 1000mL three-necked round bottom flask, add 4,7-dichloroquinoline 90g and isopropanol 141g, and heat to 60 ° C under stirring to completely dissolve slowly 95.13g of hydroxyquine side chain was added dropwise, and the timing was started after the addition was completed. The temperature was gradually increased to 120-125 ℃ over 14 hours, and then kept at 120 ℃ ～ 125 ℃ for 20 hours until the high-performance liquid detection reached the end of the reaction, waiting for the reaction After completion, the reaction solution was cooled to a temperature of 50-60 ° C, and a 6% sodium hydroxide solution was added. After alkalization, the pH value was> 12, while continuing to lower the temperature to 20-25 ° C. After the temperature was reached, 279 g of dichloromethane was added for the first time and stirred for 10 minutes. After standing for 15 minutes, the liquid was separated and the organic phase was stored. Add 198g of dichloromethane to the water phase for the second time and stir for 10 minutes. After standing for 15 minutes, separate the liquid and combine the organic phase with the previous one. Add 120g of dichloromethane to the water phase for the third time and stir for 10 minutes. After standing for 15 minutes, separate the liquid. The organic phase is combined with the previous one, and the water phase is treated as waste water. To the combined organic phase, 500 g of drinking water was added, stirred for 5 minutes, and allowed to stand for 15 minutes, and then separated. The organic phase is continuously washed with water, and the above operation is repeated several times until the pH value of the washing water is 7-8. After washing, the water temperature is controlled to 60 ° C, the internal temperature does not exceed 50 ° C, dichloromethane is distilled at atmospheric pressure, and oil is obtained after no dripping. A mixed solvent of 398 g of ethyl acetate and 61 g of isopropyl alcohol was added, and the mixture was heated and stirred to dissolve. After the dissolution is complete, 6.4 g of activated carbon is added and the temperature is slowly raised to 80 ° C. and refluxed for 1 hour. The filter cake is washed with a mixed solvent of 39 g of ethyl acetate and 6.3 g of isopropanol, and combined with the previous one. The filtrate was slowly cooled to 15-20 ° C, and the crystallization was started for 5 hours. The temperature was lowered to 0-5 ° C. After 4 hours of incubation and filtration, the filter cake was washed with a small amount of ethyl acetate to obtain a hydroxychloroquine wet product. The vacuum oven was 40 ° C. Drying within to obtain a dry product, hydroxychloroquine HPLC purity 97.8%, maximum single impurity 0.88%, yield

55%;

[0085] b. Preparation of hydroxychloroquine sulfate

[0086] Calculate the amount of raw materials based on the theoretical amount of hydroxychloroquine sulfate 129g; in a 1000mL three-necked round bottom flask, add 100g of hydroxychloroquine obtained in step a, 100g of ethyl acetate, and 500g of ethanol to stir to completely dissolve. After the dissolution is complete, the mechanical impurities are removed by filtration. The temperature was lowered to below 5 ° C, and 26g of concentrated sulfuric acid was added dropwise, and the temperature was controlled within 20 ° C. Slowly warm to 61 ° C and react for 6 hours. After the reaction is completed, the temperature is lowered to 0 ~ 5 ° C, the crystallized material is kept for 4 hours and then filtered. The filter cake is washed with a small amount of ethyl acetate to obtain hydroxychloroquine sulfate wet product, and dried in a vacuum oven at 40 ° C to obtain a dry product. The purity is 98.4%, the largest single impurity is 0.67%, and the yield is 92%.

[0087] There are 2 steps from the starting material to the final product, and the total yield is 50.6%.

[0088] Investigation table of reaction time and hydroxychloroquine quality:

[0089]

[0090] It can be seen from the table above that the temperature rise time under the control temperature below 120 ° C is 7-12h, and the reaction time at 120-125 ° C is 13-18h, which can ensure that hydroxychloroquine obtains a higher or relatively high purity and yield.

[0091] It should be noted that the above embodiments are only used to illustrate the technical solutions of the present invention and not to limit them. Although the present invention has been described by referring to the preferred embodiments of the present invention, those of ordinary skill in the art should understand that Various changes are made to it in detail and in detail without departing from the spirit and scope of the present invention.

CN104230803
Preparation method of hydroxychloroquine sulfate
[PDF]

Abstract
The invention discloses a preparation method of hydroxychloroquine sulfate. The preparation method is characterized by comprising the following steps: condensing 4,7-dichloroquinoline serving as an initial raw material and a hydroxychloroquine side chain under the action of a catalyst, so as to obtain hydroxychloroquine; and reacting hydroxychloroquine with sulfuric acid, so as to prepare the hydroxychloroquine sulfate. According to the method disclosed by the invention, the defects in the prior art are overcome. The method has the advantages that the yield of the prepared hydroxychloroquine sulfate crude product is greater than or equal to 85%, the yield of hydroxychloroquine sulfate is greater than or equal to 94%; the total yield is greater than or equal to 80%; the purity of the prepared hydroxychloroquine sulfate HPLC is greater than or equal to 99.6%; the maximum single impurity is smaller than 0.1%; the

method accords with the requirements of United States pharmacopeia, is short in reaction step, and simple in the whole technological operation; and the obtained product is high in quality, high in yield, and relatively suitable for industrial production.

[0002] The invention belongs to the technical field of medicine and chemical industry, and particularly relates to hydroxychloroquine sulfate for treating discoid lupus erythematosus and systemic lupus erythematosus.

[0003] Background technique

[0004] Hydroxychloroquine Sulfate is chemically known as 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol sulfate, CAS No. 747-36-4, The chemical structure is as follows:

[0005]

[0006] Hydroxychloroquine sulfate was successfully developed by Winthrop and first listed in the United States in 1956. It was later listed in France, Denmark, Japan, Germany, Finland and other countries and regions. On May 29, 1998, the US FDA approved hydroxychloroquine sulphate tablets for the treatment of lupus erythematosus and rheumatoid arthritis.

[0007] **US 2,546,658** discloses a process for the synthesis of hydroxychloroquine sulfate, the process of which is as follows:

[0008]

[0009] The patent was reported in 1951, using a large amount of phenol as a reaction catalyst. Phenol is toxic and corrosive. Its concentrated solution is highly corrosive to the skin. The post-treatment wastewater causes great pressure on the treatment of three wastes, and the phenol-containing wastewater It is a kind of waste that is very hazardous in industrial wastewater and difficult to handle. It is one of the wastewaters that are currently controlled in China, and the environmental pollution is particularly large. The melting point of phenol is 42 ° C, which is solid at normal temperature, and must be heated to liquid to be fed. This process is very cumbersome, unsuitable for industrialization, and the yield is also low.

[0010] **CA2561987** discloses a method for preparing hydroxychloroquine sulfate, which comprises adding 4,7-dichloroquinoline, hydroxychloroquine side chain and isopropanol in sequence, followed by stirring and heating, stirring at 120 ° C ~ 130 ° C for 20-24 hours, then Add water and methyl isobutyl ketone, adjust pH=10~11, separate the liquid, add acetic anhydride and stir at room temperature overnight, then add LiOH-H2O, water and methanol in turn, stir again at room temperature overnight, then wash once, organic layer Add methanol and sulfuric acid, stir at 35 ° C ~ 45 ° C for 3-4 hours, then cool to 20 ° C ~ 25 ° C, filtered to obtain crude hydroxychloroquine sulfate, yield 80%; then add the crude product obtained above, Water and methyl isobutyl ketone, stir and dissolve, cool to 0 ° C ~ 5 ° C, add sodium hydroxide solution to pH = 10.5 ~ 11.0, stir at room temperature for 0.5 ~ 1 hour, liquid separation, organic layer added 5% After washing with sodium chloride solution, activated carbon was added, stirred at room temperature, filtered, and the filtrate was evaporated to give hydroxychloroquine. Then, it is salted with concentrated sulfuric acid in an anhydrous alcohol solvent to obtain a hydroxychloroquine sulfate product. The purification process of

hydroxychloroquine and its sulfate in this method is very complicated, the reaction time of the whole route is particularly long, and a large amount of waste water is generated. In the post-treatment, a complicated post-treatment process is carried out in order to remove impurities, and finally the single impurity is controlled at 0.1. Below %, there are cumbersome operations, high cost, and long time, which is not conducive to industrial production. The salt forming process is to directly add concentrated sulfuric acid to an anhydrous alcohol solvent, and there is a risk of producing toxic substances such as dimethyl sulfate and diethyl sulfate.

[0011] **W02010027150** also discloses a method for synthesizing hydroxychloroquine sulfate, the reaction route of which is as follows:

[0012]

[0013] The method comprises the steps of sequentially adding 4,7-dichloroquinoline and hydroxychloroquine side chain, and applying nitrogen or argon gas to a pressure of 5 to 20 bar, and then reacting at 100 ° C to 120 ° C for 4 to 6 hours. After the reaction is completed, the product is dissolved in dilute hydrochloric acid and chloroform, and the product is dissolved in an aqueous phase, and the liquid phase is collected. The aqueous phase is collected, alkalized with sodium hydroxide, extracted with chloroform, and the chloroform layer is concentrated and then recrystallized from dichloroethane. Hydroxychloroquine products. Hydroxychloroquine is then added to the concentrated sulfuric acid under anhydrous ethanol as a solvent to obtain hydroxychloroquine sulfate. The method is carried out under high pressure, and there is a certain safety hazard, and the alkalization loss is great after acidification first, and a highly toxic solvent such as chloroform and dichloroethane is also used, which is difficult to remove in the hydroxychloroquine sulfate product. According to the ICH (International Coordinating Committee for the Registration of Technical Requirements for Human Drugs), the requirements for the Guideline for Residual Solvents, dichloroethane is the first type of solvent and should be strictly prohibited. Chloroform is the second type of solvent and should be controlled. Moreover, the limit is 60 ppm, and it is difficult to completely remove the two types of solvents in the finished product.

[0014] **CN 103724261** A discloses an industrialization method of hydroxychloroquine sulfate: the temperature reaction is directly added to the side chain of 4,7-dichloroquinoline and hydroxychloroquine under the protection of an inert gas, and the reaction is gradually heated to 120 ° C to 130 ° C during the reaction. After 13 to 24 hours, the mixture is acidified, and the excess liquid is alkalized and then layered, and crystallized by adding an organic solvent to obtain hydroxychloroquine. The method directly raises the temperature of the two raw materials, and the reaction is too strong, and a large amount of impurities are generated. After the post-treatment, acidification, a large amount of liquid alkali alkalization, and then an organic solvent is added, so that the organic layer contains a large amount of alkali liquid and inorganic The salt, the crude hydroxychloroquine crystallized after cooling, contains a large amount of inorganic salts and impurities, so that the crude purity of hydroxychloroquine is only 96%, so that the quality of hydroxychloroquine obtained directly through one salt formation is often unqualified.

[0015] In the preparation method of the above-disclosed hydroxychloroquine sulfate, there are some insufficient factors, and it is not suitable for industrial production; and most processes use toxic solvents such as chloroform and dichloroethane to obtain hydroxychloroquine sulfate, which leads to The product contains halogenated hydrocarbon

genotoxic impurities such as chloroform and dichloroethane, which does not meet the requirements of the ICH Guidelines for Residual Solvents. In the case of hydroxychloroquine sulfate formation, most of the process uses concentrated sulfuric acid under anhydrous alcohol conditions, which may present the risk of producing dimethyl sulfate and diethyl sulfate. Therefore, it is very necessary to find an industrial preparation method which is simple in operation, high in efficiency, safe and environmentally friendly, high in yield and quality, and low in production cost. The invention has been completed for this purpose.

[0016] Summary of the invention

[0017] The object of the present invention is to provide a method for preparing hydroxychloroquine sulfate, wherein 4,7-dichloroquinoline and hydroxychloroquine side chain are condensed by distillation of an acetate-based organic solvent under the action of a sodium alkoxide catalyst. The reaction is subjected to alkalization, extraction with an organic solvent of an acetate, washing, and crystallization to obtain hydroxychloroquine, and then hydroxychloroquine is reacted with sulfuric acid in a mixed solvent system containing at least water and an alcohol to obtain hydroxychloroquine sulfate. The reaction route is as follows:

[0018]

[0019] 1、The molar ratio of 4,7-dichloroquinoline to hydroxychloroquine side chain is 1:1.05.

[0020] 2、The catalyst is sodium alkoxide, such as sodium methoxide, sodium ethoxide, sodium t-butoxide, sodium t-amylate, etc., and the molar ratio of the catalyst to 4,7-dichloroquinoline is 0.2:1.

[0021] 3、The acetate organic solvent is isopropyl acetate or t-butyl acetate, and among them, isopropyl acetate is preferred. (Amount: 5-6 times the weight of 4,7-dichloroquinoline)

[0022] 4、The heating method is: after heating the reaction liquid to the reflux temperature, the solvent is distilled off, and the temperature is gradually raised to 110 ° C for 9 to 10 hours, then the temperature is raised to 120 ° C to 122 ° C for 10 to 12 hours, and finally the temperature is maintained at 120 ° C to 122 ° C. 4~5 hours.

[0023] 5、The alkalization mode is as follows: the reaction solution is slightly cold and directly alkalized with a 5% sodium hydroxide solution.

[0024] 6、The crystallization method is: after the extracted acetate solvent is washed with water, the total addition amount is 20% to 30%, and then the crystal is naturally cooled, and the crystallization temperature is 0 ° C to 30 ° C.

[0025] 7、The process of forming a salt of hydroxychloroquine and sulfuric acid in a dilute alcohol solution is as follows: hydroxychloroquine is dissolved in a mixed solvent containing at least 4 times of water and an alcohol, and concentrated sulfuric acid is added dropwise at 0° C. to 10° C. to pH=4.5~ 5.5, keep warm at 20 ° C ~ 30 ° C for 2 ~ 3 hours, cool to 0 ° C ~ 10 ° C filtered to obtain hydroxychloroquine sulfate.

[0026] The 4,7-dichloroquinoline and hydroxychloroquine side chains used in the present invention are industrial raw materials which are commercially available on a large scale; and

the solvents used are industrial raw materials.

[0027] The "hydroxychloroquine side chain" referred to in the present invention means the starting material "5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine"; "sodium alkoxide" means an alkane A base formed by replacing a hydrogen of a base alcohol with sodium; "acetate" means an ester of acetic acid with a monohydric alcohol. "95% ethanol" means that the volume ratio of absolute ethanol to purified water is 95:5, and industrial 95% ethanol can be directly purchased on the market.

[0028] The advantages of the invention are as follows:

[0029] 1)In the production process, a single organic solvent is used for reaction, extraction and crystallization, which avoids the use of toxic solvents such as chloroform and dichloroethane. On the one hand, it saves production costs, can be recycled, and on the other hand reduces environmental pollution.

[0030] 2)Avoid the use of toxic catalyst phenol, the reaction is carried out under normal pressure, avoiding the danger of high pressure reaction.

[0031] 3)In the post-reaction treatment, direct alkalization, simple operation, reducing the amount of liquid alkali, reducing the number of water washing, reducing the amount of wastewater generated.

[0032] 4)Crystallized by isopropyl acetate or tert-butyl acetate, the granular crystals are precipitated at room temperature, the melting point is 89 ° C ~ 91 ° C, the crystal habit is good, the product impurity content is low, filtration and drying fast, avoiding the crystallization after mixing solvent Solvents are not well recycled, and many solvents crystallize without crystals.

[0033] 5)The crude hydroxychloroquine is directly salted with sulfuric acid, using an aqueous mixed solvent of alcohol to avoid the risk of producing toxic substances under anhydrous conditions.

[0034] 6)The yield of the crude hydroxychloroquine obtained by the invention is ≥85% (based on 4,7-dichloroquinoline, the same below), the purity of hydroxychloroquine HPLC is ≥99.0%; the yield of salt formation is ≥94% (according to hydroxychloroquine, the same The purity of hydroxychloroquine sulfate is HPLC≥99.6%, the maximum single impurity is <0.1%, and the melting point is 239°C~241°C.

[0035] The preparation of the hydroxychloroquine sulfate industrialization of the present invention is further illustrated and explained below by way of examples without limiting the scope of the invention.

[0036] Detailed ways

[0037] Example 1 Preparation of Hydroxychloroquine Sulfate

[0038] 1.1 Preparation of hydroxychloroquine

[0039] In a three-necked round bottom flask, 4,7-dichloroquinoline (198.0 g, 1.0 mol),

hydroxychloroquine side chain (182.7 g, 1.05 mol) and isopropyl acetate 1089 g were added, and sodium ethoxide (13.6 g, was slowly added. 0.2mol), slowly heated to reflux under stirring conditions, then distilled off isopropyl acetate, gradually heated to 110 ° C over 9 hours, then heated to 120 ° C ~ 122 ° C 10 hours, and finally 120 ° C ~ 122 ° C reaction After 4 hours, after the reaction was completed, the reaction solution was cooled to 90 ° C to 100 ° C, directly added to a 5% sodium hydroxide solution, and alkalized to pH = 9 to 10. The distilled isopropyl acetate was extracted twice, and the layers were separated. 500 g of drinking water was added to the combined organic phase, washed, layered, and the above operation was repeated until the pH of the washing water was 7. After the washing was completed, the water temperature was controlled to 65 ° C, and 200 to 300 g of isopropyl acetate was distilled off under reduced pressure. Then, 9.9 g of activated carbon was added, and the mixture was heated under reflux for 1 hour, filtered while hot, the filtrate was cooled to 0 ° C, and the mixture was filtered for 2 hours, filtered, and dried at 60 ° C for 4 hours to obtain 294.6 g of crude hydroxychloroquine. The melting point is 89.2 ° C ~ 91.3 ° C, HPLC purity 99.3%, the largest single impurity <0.1%, the yield of 87.7%.

[0040] 1.2 Preparation of hydroxychloroquine sulfate

[0041] In a three-necked round bottom flask, 100 g of hydroxychloroquine obtained in Example 1.1 and 500 g of 95% ethanol were added. After the dissolution was completed, the temperature was lowered to 0 ° C to 10 ° C, and concentrated sulfuric acid was slowly added thereto to adjust the pH to 4.5 to 5.5, and the temperature was controlled. Within 10 °C. Then, the reaction was kept at 20 ° C to 30 ° C for 3 hours. After the reaction was completed, the temperature was lowered to 0 ° C to 10 ° C for 2 hours, and then filtered, and dried under reduced pressure to obtain 123.0 g of hydroxychloroquine sulfate, melting point of 239.8 ° C to 240.5 ° C, HPLC purity. 99.6%, the largest single impurity <0.1%, the yield is 95.2%.

[0042] Example 2 Preparation of Hydroxychloroquine Sulfate

[0043] 2.1 Preparation of hydroxychloroquine

[0044] According to the embodiment 1.1, the type of the catalyst is changed, the reaction effect after the dosage is not changed, and other conditions are unchanged, and the obtained results are as follows:

[0045] table 2-1

[0046]

[0047] 2.2 Preparation of hydroxychloroquine sulfate

[0048] Based on Example 1.2, the salt formation reaction was carried out using the hydroxychloroquine obtained in Example 2.1, and the other conditions were unchanged. The results are as follows:

[0049] Table 2-2

[0050]

[0051] Example 3 Preparation of Hydroxychloroquine Sulfate

[0052] 3.1Preparation of hydroxychloroquine

[0053] In a three-necked round bottom flask, 4,7-dichloroquinoline (198.0 g, 1.0 mol), hydroxychloroquine side chain (182.7 g, 1.05 mol) and tert-butyl acetate 1089 g were added, and sodium ethoxide (13.6 g, 0.2mol), slowly heated to reflux under stirring conditions, then by distillation of t-butyl acetate, gradually heated to 110 ° C over 9 hours, then heated to 120 ° C ~ 122 ° C 10 hours, and finally 120 ° C ~ 122 ° C reaction After 4 hours, after the reaction was completed, the reaction solution was cooled to 90 ° C to 100 ° C, and 5% sodium hydroxide solution was added thereto, and alkalized to pH = 9 to 10. The distilled t-butyl acetate was extracted twice, and the layers were separated. 500 g of drinking water was added to the combined organic phase, washed, layered, and the above operation was repeated until the pH of the washing water was 7. After the completion of the washing, the temperature of the water was controlled to 65 ° C, and 200 to 300 g of t-butyl acetate was distilled off under reduced pressure. Then, 9.9 g of activated carbon was added, and the mixture was heated under reflux for 1 hour, and filtered hot. The filtrate was naturally cooled to 30 ° C, and after crystallization for 2 hours, it was filtered, and dried at 65 ° C for 4 hours to obtain 285.3 g of crude hydroxychloroquine. The melting point is 89.4 ° C ~ 91.0 ° C, HPLC purity 99.1%, the maximum single impurity <0.1%, the yield of 85.1%.

[0054] 3.2 Preparation of hydroxychloroquine sulfate

[0055] In a three-necked round bottom flask, 100 g of hydroxychloroquine obtained in Example 3.1 and 400 g of 95% ethanol were added. After the dissolution was completed, the temperature was lowered to 0 ° C to 10 ° C, and concentrated sulfuric acid was slowly added dropwise to adjust the pH to 4.5 to 5.5, and the temperature was controlled. Within 10 °C. Then, the reaction was kept at 20 ° C to 30 ° C for 3 hours. After the reaction was completed, the temperature was lowered to 0 ° C to 10 ° C for 2 hours, and then filtered, and dried under reduced pressure to give 122.7 g of hydroxychloroquine sulfate. The melting point is 239.4 ° C ~ 240.6 ° C, the HPLC purity is 99.6%, the maximum single impurity is <0.1%, and the yield is 95.0%.

[0056] Example 4 Preparation of Hydroxychloroquine Sulfate

[0057] 4.1 Preparation of hydroxychloroquine

[0058] According to the embodiment 3.1, the type of the catalyst is changed, the reaction effect after the dosage is not changed, and other conditions are unchanged, and the obtained results are as follows:

[0059] Table 4-1

[0060]

[0061] 4.2 Preparation of hydroxychloroquine sulfate

[0062] Based on Example 3.2, the salt formation reaction was carried out using the hydroxychloroquine obtained in Example 4.1, and the other conditions were unchanged. The results are as follows:

[0063] Table 4-2

[0064]

[0065] Example 5 Preparation of Hydroxychloroquine Sulfate

[0066] 5.1Preparation of hydroxychloroquine

[0067] In a three-necked round bottom flask, 4,7-dichloroquinoline (99. 0 g, 0.5 mol), hydroxychloroquine side chain (91.5 g, 0.525 mol) and isopropyl acetate 545 g were added, and sodium t-amylate was slowly added (11.0g, 0.1mol), slowly heated to reflux under stirring conditions, and then distilled isopropyl acetate, gradually heated to 110 ° C over 9 hours, then heated to 120 ° C ~ 122 ° C 10 hours, and finally maintained 120 ° C ~ After reacting at 122 ° C for 4 hours, after the reaction was completed, the reaction solution was cooled to 90 ° C to 100 ° C, and 5% sodium hydroxide solution was added thereto to alkalinize to pH = 9 to 10. The distilled isopropyl acetate was extracted twice, and the layers were separated. 250 g of drinking water was added to the combined organic phase, washed, layered, and the above operation was repeated until the pH of the washing water was 7. After the washing was completed, the temperature of the water was controlled to 65 ° C, and 100 to 150 g of isopropyl acetate was distilled off under reduced pressure. Then, 5.0 g of activated carbon was added, and the mixture was heated under reflux for 1 hour, and filtered while hot. The filtrate was naturally cooled to 15 ° C, and the mixture was allowed to stand for 2 hours, filtered, and dried at 65 ° C for 4 hours to obtain 149.0 g of crude hydroxychloroquine. The melting point is 89.4 ° C ~ 91.5 ° C, HPLC purity 99.5%, the largest single impurity <0.1%, yield 88.9%.

[0068] 5.2 Preparation of hydroxychloroquine sulfate

[0069] In a three-necked round bottom flask, 10.0 g of hydroxychloroquine obtained in Example 5.1 and 40.0 g of 95% ethanol were added. After the dissolution was completed, the temperature was lowered to 0 ° C to 10 ° C, and concentrated sulfuric acid was slowly added thereto to adjust the pH to 4.5 to 5.5. The temperature is within 10 °C. Then, the reaction was kept at 20 ° C to 30 ° C for 3 hours, and after the reaction was completed, the temperature was lowered to 0 ° C to 10 ° C for 2 hours, and then filtered, and dried under reduced pressure to obtain 12.4 g of hydroxychloroquine sulfate, melting point of 239.5 ° C to 240.5 ° C, HPLC purity. 99.8%, the largest single impurity <0.1%, the yield is 96.1%.

[0070] Example 6 Preparation of Hydroxychloroquine Sulfate

[0071] Based on Example 5.2, the hydroxychloroquine obtained in Example 5.1 was used to carry out the salt formation reaction, and the solvent was changed. The other conditions were unchanged, and the results were as follows:

[0072] Table 6-1

[0073]

[0074] The invention has been described in detail above, including its preferred embodiments. It is to be understood, however, that the invention may be modified and/or modified within the spirit and scope of the appended claims.

CN107266323

Side chain, synthesis method thereof, and method for synthesizing hydroxychloroquine sulfate from side chain

[PDF]

Abstract

The invention discloses a side chain, a synthesis method thereof, and a method for synthesizing hydroxychloroquine sulfate from the side chain. The synthesis method of the side chain comprises the following steps: 1, condensing N-ethylethanolamine and 5-chloro-2-pentanone to obtain a condensation product; 2, esterifying the condensation product and an acetyl reagent to obtain an esterification product; 3, reducing the esterification product to obtain a reduction product; and 4, reacting the reduction product with a halogenating agent to obtain the side chain. The synthesis method of the hydroxychloroquine sulfate comprises the following steps: 1, reacting 4-amino-7-chloroquinoline with paratoluensulfonyl chloride to obtain 4-Tos-amino-7-chloroquinoline; 2, reacting the side chain with the 4-Tos-amino-7-chloroquinoline to obtain a hydroxyquine base; and 3, reacting the hydroxyquine base with sulfuric acid to obtain the hydroxychloroquine sulfate. The synthesis method of the new side chain avoids the ammonification process and the catalytic hydrogenation process, and is safe and environmentally friendly, and the hydroxychloroquine sulfate can be obtained through low-temperature condensation of the side chain, so the quality of the above products is remarkably improved, and the production flow is simplified.

[0001] Technical field

[0002] The invention belongs to the field of medicine and chemical industry, in particular to a side chain and a synthesis method thereof, and a method for synthesizing hydroxychloroquine sulfate using the side chain.

[0003] Background technique

[0004] Hydroxychloroquine sulfate, chemical name 2-4- (7-chloro-4-quinolyl) aminopentylethylamino-ethanol sulfate, English name: Hydroxychloroquine Sulfate, the chemical structure is as follows:

[0005]

[0006] Hydroxychloroquine (HCQ) is an anti-malarial drug consisting of 4-aminoquinoline compounds, synthesized in 1946 by Surrey and Hammer. Clinic for the treatment of discoid lupus erythematosus and systemic lupus erythematosus, has also been widely used in rheumatoid-related diseases.

[0007] Discoid lupus erythematosus (DLE) is a common skin and mucous membrane connective tissue disease, 25% -35% have oral damage, can be issued in the mouth without incidental skin damage, and more no obvious systemic symptoms. The etiology and pathogenesis is not yet clear, the treatment is more difficult, easy to relapse and cancer. Traditional application of chloroquine phosphate (CQ) for the treatment of DLE, but the side effects. HCQ has anti-inflammatory, anti-amine and immunosuppressive effects, reducing lymphocyte conversion, inhibiting vascular permeability, stabilizing lysosomal membranes, so the treatment of DLE with HCQ targeted. So far, HCQ is considered more secure than CQ.

A large number of clinical and literature reports confirmed the use of hydroxychloroquine sulfate (HCQ) treatment of DLE obtained satisfactory results.

[0008] Systemic Lupus Erythematosus (SLE) is a multi-systemic disease with many kinds of antibodies in the body. The etiology and treatment are difficult and difficult to treat. While antimalarial drugs used to treat SLE began in 1950, Dobois found that after 75% -80% of SLE patients were treated with antimalarial drugs, rashes, fever, and joint symptoms improved, especially for skin lesions. Subsequent research found that anti-malarial drugs can reduce or stop the use of corticosteroids in patients with SLE and have anti-allergic effects. A double-blind controlled study by Hydroxychloro in Canada showed that HCQ can stabilize SLE patients and significantly reduce recurrence. Wallace et al found that HCQ treatment can reduce the level of blood lipid in patients with corticosteroid-dependent, can significantly reduce the incidence of thrombosis. Given that HCQ can have a beneficial effect on SLE, most scholars advocate that HCQ is used in patients with mild to moderate SLE, combined with hormones and immunosuppressants for adjuvant treatment of severe SLE.

[0009] 90% of foreign countries choose hydroxychloroquine when applying anti-malarial drugs to treat SLE, while domestic may be affected by such factors as cognition and drug source, and most choose chloroquine. In fact, from a security point of view, if the patient's condition allows, do not need to rely on antimalarial drugs in a short period of time to play a curative effect, should try to choose hydroxychloroquine.

[0010] As scientists further study found that hydroxychloroquine can play a variety of immune regulation in rheumatic diseases, the preferred hydroxychloroquine has a significant anti-inflammatory effect, it can stabilize the lysosome, inhibit enzyme activity, thereby inhibiting the activation of inflammatory mediators , While inhibiting the chemotaxis and infiltration of inflammatory cells such as neutrophils and significantly reducing the production of proinflammatory cytokines such as TNF-α, IL-1 and IL-6; second, hydroxychloroquine can inhibit the growth of fibroblasts And connective tissue deposition and thus inhibit synovial hyperplasia in patients with arthritis; hydroxychloroquine can inhibit the interaction of antigen and antibody and immune complex synthesis, to reduce the titer of rheumatoid factor; hydroxychloroquine can also affect the absorption of ultraviolet light and block UV damage to the skin. All of the above are hydroxychloroquine in clinical treatment of rheumatic diseases provide a large number of basis. In addition, many centers of large-scale clinical studies also confirmed hydroxychloroquine in the treatment of rheumatism play a significant therapeutic effect.

[0011] At present, the synthesis of hydroxychloroquine sulfuric acid generally take the following synthetic route:

[0012]

[0013] The core of this route is that 5- (N-ethyl-N-2-hydroxyethylamine) -2-pentanamine (hereinafter abbreviated hydroxychloroquine side chain) and 4,7- Preparation of hydroxychloroquine base reaction, and then salt with sulfuric acid. US2546658 discloses a method for synthesizing hydroxychloroquine sulfate, the reaction process is as follows:

[0014]

[0015] The process is older, the use of phenol as a solvent, phenol is toxic and corrosive,

serious environmental pollution, post-processing complex, not suitable for industrial production, and the yield is relatively low, below 20%.

[0016] CA2561987 discloses a method for synthesizing hydroxychloroquine sulfate, the reaction process is as follows:

[0017]

[0018] The method establishes the basic conditions for improving the yield of hydroxyquinoline base of hydroxychloroquine side chain and 4,7-dichloroquinoline, ie high temperature reaction. Although the purity of the product is above 99.5%, the solvent isobutyl Ketones and reagents Lithium hydroxide high prices, high cost of raw materials, and cumbersome methods of operation, a long time, is not conducive to industrial production.

[0019] **WO2010027150** also discloses a method for synthesizing hydroxychloroquine sulfate. The reaction process is as follows:

[0020]

[0021] The law is still high temperature reaction, and the need for high-pressure reaction, a higher security risk.

[0022] **CN103724261A** discloses a new industrial hydroxy hydroxy quinoline sulfate method, the reaction process is as follows:

[0023]

[0024] The method uses inert gas to reduce the risk of oxidation impurities, but it is still a high temperature reaction. The side reactions such as dehydration and condensation can not be avoided and the corresponding impurities still exist. The purity of the reported HPLC can only ensure ≧ 99.2%.

[0025] Hydroxychloroquine side chain is the synthesis of hydroxychloroquine sulfate key intermediates, reported in the literature there are two synthetic methods: Route one is the first 5-chloro-2-pentanone first prepared as a ketal, and then N-ethyl ethanolamine Reaction to give 5- (N-ethyl-N-2-hydroxyethylamine) -2-pentanone, and then by ammoniation, hydrogenation hydroxychloroquine side chain; Route two, Reaction of pentanone with N-ethylethanolamine gives 5- (N-ethyl-N-2-hydroxyethylamine) -2-pentanone, which is then aminated and hydrogenated to reduce the hydroxychloroquine side chain. Ammonia or high concentration of liquid ammonia is required for both routes. Ammonia or high concentration of liquid ammonia is required, and the odor is heavy, adversely affecting the environment. Simultaneously, the imine is subjected to high pressure hydrogenation to prepare an amino group, which has a high safety risk. In 2015, CN104803859A disclosed a method for synthesizing 5- (N-ethyl-N-2-hydroxyethylamine) -2-pentylamine, that is, a method for synthesizing hydroxychloroquine side chain. The synthetic route is as follows:

[0026]

[0027] In summary, the current synthesis of hydroxychloroquine sulfate there are two main adverse factors: First, hydroxychloroquine side chain preparation: the need to use ammonia

or high concentrations of liquid ammonia, heavy smell, the adverse impact on the environment, while imine Need high-pressure hydrogenation to reduce the amino group, the safety risk is high; Second, hydroxychloroquine base preparation: 4,7-Dichloroquinoline 4 chlorine activity is relatively low, and can not only use catalysts such as potassium bromide, potassium iodide catalytic , Therefore, it is necessary to react under high temperature. During the reaction of high temperature, -NH2 and -OH at the end of hydroxychloroquine side chain are easily oxidized, dehydrated, condensed and so on. Therefore, if it is necessary to ensure the product quality, a relatively complicated post-treatment process And use a lot of organic solvents. In addition, the existing synthetic route also has the defects of long production cycle, high impurity content, low yield and high raw material cost. Therefore, it is of great social significance and significant economic value to design an industrialized synthetic route with simple process, mild reaction conditions, high safety and environmental protection, high yield and high quality, and low manufacturing cost.

[0028] Content of the invention

[0029] The purpose of the present invention is to provide a side chain and a method for synthesizing the same, and a method for synthesizing hydroxychloroquine sulfate using the side chain. The method for synthesizing the side chain can avoid the use of ammonia or high-concentration liquid ammonia on the one hand and does not require high pressure On the other hand, the synthesized new side chain replaces the hydroxychloroquine side chain, and the hydroxychloroquine sulfate can be synthesized at the lower reaction temperature, which can avoid hydroxychloroquine side chain -NH2 and -OH reaction occurs under high temperature conditions, help to ensure product quality, and does not require cumbersome after-treatment process.

[0030] The technical solution adopted by the present invention is as follows:

[0031] A side chain of the formula:

[0032] Where R is Cl, Br or I.

[0033] A side chain synthesis method, comprising the following steps:

[0034] (1)Condensation reaction: adding N-ethylethanolamine, phase transfer catalyst, inorganic alkali and organic solvent to water, controlling the temperature to be 20-30 DEG C, adding dropwise 5-chloro-2-pentanone for 2-6 hours, Layer, take the organic layer was dried to obtain the condensation product of the organic phase, the chemical name of the condensation product is: 5- (N-ethyl-N-2-hydroxyethyl amine) -2-pentanone;

[0035] (2)Esterification reaction: the condensation product is cooled to 0 to 10 DEG C in an organic phase, and incubated for 1 to 3 hours under the condition of dropwise addition of an acetyl reagent for incubation. After the reaction is completed, the organic layer is layered and washed with water, and the organic phase of the esterified product is obtained. The chemical name of the product is: 5- (N-ethyl-N-2-acetoxyamine) -2-pentanone;

[0036] (3)Reduction reaction: the esterified product was cooled to -5 ~ 0 ° C in an organic phase, reacted with a reducing agent for 1 to 4 hours, added with water, layered, and the organic layer was dried to obtain the chemical product of the reduced product Is: 5- (N-ethyl-N-2-acetoxyamine) -2-methylpentanol;

[0037] (4)Halogenation reaction: Adding the catalyst into the organic phase of the reduction product, controlling the temperature to 25-40 DEG C, reacting the halogenated reagent dropwise for 3 to 8 hours while keeping the temperature, delaminating and washing with water, and taking the organic layer to dry to obtain the side chain organic phase; The chemical name of the chain is: 5- (N-ethyl-N-2-acetoxyamine) -2-chloropentane.

[0038] Further, before the esterification reaction and the halogenation reaction are stratified by the completion of the reaction, it is necessary to add the reaction system to an aqueous solution of an inorganic alkali to neutralize the acid formed during the esterification reaction and the halogenation reaction, , Washed with water to ensure that the finally generated side chain organic phase does not contain acid, alkali and other impurities, preferably 0 to 5 ° C., and can cool the reaction system for the subsequent reaction.

[0039] In the step (1), the molar ratio of 5-chloro-2-pentanone to N-ethylethanolamine is 0.8 to 1.2, and the molar ratio of the inorganic base to 5-chloro-2-pentanone is 1.2 to 1.8.

[0040] More preferably, the molar ratio of 5-chloro-2-pentanone to N-ethylethanolamine is from 0.8 to 1.0 and the molar ratio of inorganic base to N-ethylethanolamine is from 1.2 to 1.5. In this step, the molar ratio of 5-chloro-2-pentanone and N-ethylethanolamine is designed to be 0.8-1.0, which is favorable for the complete conversion of 5-chloro-2-pentanone, the reduction of the residue in the organic phase and the increase of the condensation Product purity and content, reduce the formation of impurities, the molar amount of inorganic base slightly more than 5-chloro-2-pentanone molar amount can be, both to ensure the catalytic, the amount of acid, but also not waste, but also reduce waste emission.

[0041] In the step (1), the phase transfer catalyst is tetrabutylammonium bromide, tetrabutylammonium hydrogen sulfate, tetrabutylammonium chloride, trioctylmethylammonium chloride, dodecyltrimethyl Ammonium chloride or tetradecyltrimethylammonium chloride. In this step, N-ethylethanolamine is dissolved in water and 5-chloro-2-pentanone is dissolved in organic solvent. Therefore, the reaction system is a mixed system of aqueous phase and organic phase and belongs to the heterophasic system. In the ion binding, and use their own affinity for organic solvents, the N-ethyl ethanolamine in the aqueous phase transferred to the organic phase, prompting the reaction to occur, thereby accelerating the heterogeneous system reaction rate.

[0042] More preferably, the phase transfer catalyst is tetrabutylammonium bromide.

[0043] In the step (1), the organic solvent is dichloromethane, chloroform or chlorobenzene.

[0044] More preferably, the organic solvent is chloroform.

[0045] Further, in the step (2), the molar ratio of the acetyl reagent to the condensation product is from 1.0 to 1.5.

[0046] In the step (2), the acetyl reagent is acetyl chloride or acetic anhydride. Acetylation is the condensation of the end product - OH introduction of acetyl CH3CO- reaction, with high product conversion, mild reaction conditions, environmental protection and other characteristics, commonly used acetyl reagent acetyl chloride or acetic anhydride.

[0047] More preferably, the acetyl reagent is acetyl chloride, which has the fastest reaction

rate.

[0048] Further, in the step (2), the concentration of the inorganic alkali aqueous solution is 5 to 10%, and the amount thereof is 0.5 to 2.0 times of the weight of the organic phase.

[0049] More preferably, the aqueous alkali solution is used in an amount of 1.0 to 2.0 times the weight of the organic phase.

[0050] Further, in the step (3), the molar ratio of the reducing agent to the esterified product is 0.3 to 0.5.

[0051] Further, in the step (3), the reducing agent is sodium borohydride, potassium borohydride or borane diethyl ether. Hydrogenation of hydrogenation reagent hydrogen anion release, strong alkaline, and has a strong nucleophilic ester products can be ester groups reduced to hydroxyl.

[0052] More preferably, the reducing agent is sodium borohydride, the reaction conditions are mild, cheap, more widely used.

[0053] Further, in the step (3), the temperature is lowered by using ethanol. Ethanol in addition to the esterified product of the organic phase can be rapidly cooled to the desired reaction temperature, its miscibility with organic solvents, but also promote the dissolution of reactants to speed up the reduction reaction rate.

[0054] Further, in the step (3), the amount of ethanol is 15-40% by weight of the organic solvent and the amount of the water is 0.5-2.0 times by weight of the organic solvent.

[0055] More preferably, the amount of ethanol is from 20 to 40% by weight of the organic solvent and the amount of water is from 0.5 to 1.5 times the weight of the organic solvent.

[0056] Further, in the step (4), the molar ratio of the halogenated reagent to the reduced product is 1.2 to 1.5.

[0057] In the step (4), the halogenating reagent is thionyl chloride, phosphorus trichloride, thionyl bromide, phosphorus tribromide, phosphorus pentabromide, N-chlorosuccinimide, N-Bromosuccinimide or N-iodosuccinimide. By halogenation, the hydroxyl groups in the reduced product are replaced by halogens to form the halogen substituted as the side chain for the subsequent synthesis of hydroxychloroquine sulfate.

[0058] More preferably, the halogenating agent is thionyl chloride.

[0059] Further, in the step (4), the catalyst is N, N-dimethylformamide in an amount of 0.05 to 0.2 times the weight of the halogenated reagent.

[0060] Further, in the step (4), the concentration of the inorganic alkali aqueous solution is 8 to 10%, and the amount thereof is 4.0 to 6.0 times of the weight of the organic phase.

[0061] The method for synthesizing hydroxychloroquine sulfate using the side chain comprises the following steps:

[0062] (A) N protection reaction: 4-amino-7-chloroquinoline, co-solvent was added to an organic solvent, warmed to 30 ~ 40 ° C, p-toluenesulfonyl chloride was added and reacted for 2 to 6 hours, , Recrystallization, drying 4-Tos amino-7-chloroquinoline;

[0063] (B) Condensation reaction: the catalyst and 4-Tos amino-7-chloroquinoline are added to the side chain organic phase, the temperature is raised to 60-80 DEG C, the reaction is completed, the temperature is lowered to 5-20 DEG C and the mixture is separated into layers, The organic layer is concentrated to obtain hydroxyquinoline crude, recrystallized and dried to obtain hydroxyquinoline;

[0064] More preferably, after the reaction is completed, the temperature is lowered to 5 to 10 ° C and the layers are separated.

[0065] (C) Salt-forming reaction: adding the hydroxyquinoline base to an alcoholic solvent, raising the temperature to 50-60 ° C., dissolving completely, adding sulfuric acid dropwise for 1 hour, cooling to 0-10 ° C. to obtain sulfuric acid Hydroxychloroquine.

[0066] Further, in the steps (A) and (B), the reaction system needs to be added to an aqueous solution of an inorganic base to react before stratification of the reaction is completed.

[0067] In the step (A), an aqueous solution of an inorganic alkali at 0 to 10 ° C is used. In the step (B), after the reaction is completed, the reaction system is first cooled to 20-30 ° C and then added to an aqueous solution of inorganic alkali at 20-40 ° C for 3 to 8 hours, preferably 30-40 ° C.

[0068] In the step (A), the molar ratio of p-toluenesulfonyl chloride to 4-amino-7-chloroquinoline is 1.0 to 1.2.

[0069] Further, in the step (A), the organic solvent is methylene chloride, chloroform or dichloroethane in an amount of 3 to 6 times the weight of 4-amino-7-chloroquinoline.

[0070] More preferably, the organic solvent is chloroform.

[0071] Further, in the step (A), the cosolvent is DMF, DMSO or dioxane in an amount of 0.1-0.6 times the weight of 4-amino-7-chloroquinoline.

[0072] More preferably, the co-solvent is DMF.

[0073] More preferably, the cosolvent is used in an amount of 0.1 to 0.4 times the weight of 4-amino-7-chloroquinoline.

[0074] Further, in the step (A), the mass concentration of the inorganic alkali aqueous solution is 5 to 10%, and the amount thereof is 1.0 to 2.0 times the weight of the organic phase.

[0075] In the step (A), the drying temperature is 40-70 ° C.

[0076] Further, in the step (B), the molar ratio of the side chain to 4-Tos amino-7-chloroquinoline is 1.0 to 1.5.

[0077] More preferably, the molar ratio of the side chain to 4-Tos amino-7-chloroquinoline is 1.0 to 1.2.

[0078] Further, in the step (B), the catalyst is potassium iodide, sodium iodide, tetrabutylammonium bromide, DMAP or pyridine in an amount of 0.02 to 0.1 times the weight of the side chain.

[0079] More preferably, the catalyst is tetrabutylammonium bromide.

[0080] Further, in the step (B), the concentration of the inorganic alkali aqueous solution is 5-40%, and the amount is 1.0-3.0 times the weight of the organic phase.

[0081] More preferably, the concentration of the aqueous inorganic base solution is 10-40%.

[0082] In the step (B), the drying temperature is 40-70 ° C.

[0083] Further, in the step (C), the molar ratio of sulfuric acid to hydroxyquinolyl is 1.0 to 1.1.

[0084] Further, in step (C), the alcohol solvent is 95% ethanol, methanol or absolute ethanol solution, and the dosage is 3-5 times of the weight of hydroxyquinoline.

[0085] More preferably, the solvent is 95% ethanol.

[0086] In the step (C), the crystallization time is 0.5 to 3 hours.

[0087] In the step (C), the drying temperature is 40-70 ° C.

[0088] In the above method for synthesizing the side chain and the hydroxychloroquine sulfate, the inorganic alkali used is sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium bicarbonate or potassium bicarbonate, and the inorganic alkali in step (1) is preferably The inorganic base in step (2) and step (4) is preferably sodium carbonate, and the inorganic base in step (A) and step (B) is preferably sodium hydroxide. The inorganic base in the step (1) is added as a catalyst to water together with N-ethylethanolamine, a phase transfer catalyst and an organic solvent in order to promote the condensation reaction of N-ethylethanolamine and 5-chloro-2-pentanone Process to speed up the reaction rate, preferably stronger alkaline potassium hydroxide. The inorganic bases in the subsequent steps are all present in the form of an aqueous alkali solution for neutralizing the acid formed during the reaction and for adjusting the pH wherein the products formed in steps (2) and (4) are less stable, Thus, less basic sodium carbonate is used, while the products formed in steps (A) and (B) are more stable, preferably more basic, sodium hydroxide.

[0089] In the above method for synthesizing a side chain, the method for drying is as follows: the organic layer is dried under the action of a desiccant at 10 to 20 DEG C for 1 to 2 hours, the desiccant is anhydrous sodium sulfate or anhydrous magnesium sulfate in an amount of 10 ~ 20% of organic solvent.

[0090] The reaction mechanism of the synthetic route of the present invention is:

[0091] First, N-ethylethanolamine and 5-chloro-2-pentanone are condensed, esterified, reduced and halogenated to obtain side chains. The reaction process is as follows:

[0092]

[0093] Then, 4-amino-7-chloroquinoline is reacted with p-toluenesulfonyl chloride to give 4-Tos amino-7-chloroquinoline. Finally, 4-Tos amino-7-chloroquinoline is condensed with the side chain to form a salt, Hydroxychloroquine, the reaction process is as follows:

[0094]

[0095] (Where R = Cl, Br, I, preferably -Cl)

[0096] In summary, due to the adoption of the above technical solutions, the beneficial effects of the present invention are as follows:

[0097] 1、In the invention, a novel side chain for synthesizing hydroxychloroquine sulfate is prepared by condensation, esterification, reduction and halogenation reaction of N-ethylethanolamine and 5-chloro-2-pentanone, wherein the side chain of Synthesis of non-ammoniated process, no catalytic hydrogenation process, the solvent used is easy to recycle, safety and environmental protection, and easy to operate, reducing the difficulty of industrial production;

[0098] 2、The side chain of the present invention replaces the existing hydroxychloroquine side chain and discards the conventional 4,7-dichloroquinoline instead of 4-amino-7-chloroquinoline with p-toluenesulfonyl chloride to give 4-Tos amino-7- Chloroquinoline, and the new side chain can be synthesized at low temperature hydroxychloroquine sulfate, reducing the risk of high temperature side reaction impurities, enhance the intrinsic quality of the product, simplifying the production process;

[0099] 3、The low-temperature condensation process of the invention has the advantages of low temperature and short time, is favorable for reducing energy consumption and improving equipment utilization;

[0100] 4.The invention has the advantages of simple synthesis route, mild reaction conditions, safety and environmental protection, high yield and high quality, low manufacturing cost and suitable for industrial production of hydroxychloroquine sulfate.

[0101] BRIEF DESCRIPTION OF THE DRAWINGS FIG

[0102] Figure 1 is a schematic view of the synthesis route of the present invention;

[0103] Figure 2 is an HPLC chromatogram of hydroxychloroquine sulfate sample;

[0104] Figure 3 is an HPLC chromatogram of hydroxychloroquine sulfate reference substance.

[0105] detailed description

[0106] All of the features disclosed in this specification may be combined in any manner

other than mutually exclusive features and / or steps.

[0107] The present invention will be described in detail below with reference to FIGS. 1, 2 and 3.

[0108] N-ethylethanolamine, 5-chloro-2-pentanone, 4-amino-7-chloroquinoline and p-toluenesulfonyl chloride used in the present invention, as well as the organic solvents and alcoholic solvents used are all commercially available Industrial raw materials, "95% ethanol" for the industrial 95 ethanol.

[0109] Example 1

[0110] Preparation of side chains:

[0111] (1)Condensation reaction: 30 g of N-ethylethanolamine, 0.6 g of tetrabutylammonium bromide, 25 g of potassium hydroxide, 240 g of chloroform and 120 g of water were added to a reaction flask, and then the temperature was controlled to be 20 to 30 ° C. 38 g of 5- 2-pentanone, after the addition was complete, the reaction was stirred for 3 hours, still stratified, the aqueous phase was discarded, the organic layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered, The organic phase of the condensation product was detected. The content of the condensation product was 50.2g. The molar yield was 92% (based on 5-chloro-2-pentanone) and the GC purity was ≧ 98.5%.

[0112] (2)Esterification reaction: the condensation product obtained in step (1) organic phase (condensation product 50.2g) was cooled to 0 ~ 5 ℃, 24g acetyl chloride was added dropwise, after completion of the dropwise addition, the reaction was incubated for 2 hours, the reaction is complete, the reaction The solution was slowly added to an aqueous solution of sodium carbonate (350 g, mass fraction of sodium carbonate 6%) pre-cooled to 0-5 ° C and stirred for 30 minutes. The layers were separated and the organic phase was washed with 200 g of water and the layers were separated. Water and sodium sulfate at the temperature of 10-20 DEG C, stirring and drying for 1 hour and filtering to obtain the organic phase of the esterification product. The content of the esterification product was 57.8g, the molar yield was 91.9% and the GC purity was ≧ 99.0%.

[0113] (3)Reduction reaction: 40g of ethanol is added to the organic phase (57.8g of the esterified product) of the esterified product obtained in the step (2), the temperature is decreased to -5 to 0 DEG C, 12.0g of sodium borohydride is slowly added, The reaction was 2.0 hours, 180g of water was added, stirred for 30 minutes, standing stratification, and then washed once with 100g of water, standing layered organic layer plus 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, Filtered to obtain the organic phase of the reduced product. The content of the product was measured. The content of the reduced product was 54.6 g, the molar yield was 93.6% and the GC purity was ≧ 99.0%.

[0114] (4)Halogenation reaction: 2.0g MDF was added to the organic phase of the reduction product (54.6g containing the reduction product) prepared in the step (3), the temperature was controlled at 25-40 ℃, 37.0g thionyl chloride After the addition was completed, the reaction was allowed to proceed for 4.0 hours. The reaction system was slowly added to an aqueous solution of sodium carbonate (800 g, 8% sodium carbonate) at 0-5 ° C. The layers were

separated and the organic layer was washed with 200 g of water and left to stand The organic layer was added with 24 g of anhydrous sodium sulphate and the temperature was controlled at 10-20 ° C. The mixture was stirred and dried for 1 hour and filtered to obtain a side chain organic phase with a content of 56.8 g, a molar yield of 96% and a GC purity of ≧ 99.0 %.

[0115] Example 2

[0116] Preparation of side chains:

[0117] (1)Condensation reaction: 30g of N-ethylethanolamine, 0.9g of tetrabutylammonium bromide, 25g of potassium hydroxide, 240g of chloroform and 120g of water were added into a reaction flask, and then the temperature was controlled to be between 20 and 30 DEG C and 38g of 5-chloro- 2-pentanone, after the addition was complete, the reaction was stirred for 3 hours, still stratified, the aqueous phase was discarded, the organic layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered, The organic phase of the condensation product was detected. The content of the condensation product was 50.8g, the molar yield was 93.1% (based on 5-chloro-2-pentanone) and the GC purity was ≧ 98.5%.

[0118] (2)Esterification reaction: the condensation product obtained in step (1) was cooled to 0 to 5 DEG C in the organic phase (containing the condensation product 50.8g), and 24g acetyl chloride was added dropwise to the mixture. After the addition was completed, the reaction was incubated for 2 hours, The reaction mixture was slowly added to an aqueous solution of sodium carbonate (350 g, mass fraction of sodium carbonate 6%) pre-cooled to 0-5 ° C. and stirred for 30 minutes. The layers were separated and the organic layer was washed with 200 g of water. The layers were separated and the organic layer was added with 24 g Anhydrous sodium sulfate was added. The temperature was controlled at 10 ~ 20 ℃. The mixture was stirred and dried for 1 hour. The mixture was filtered to obtain an organic phase of the esterified product. The content of the esterification product was 57.9g. The molar yield was 92.0% and the GC purity was ≧ 99.0%.

[0119] (3)Reduction reaction: 40g of ethanol was added into the organic phase (57.9g of the esterified product) of the esterified product obtained in the step (2), cooled to -5 ~ 0 ℃, 12.0g of sodium borohydride was slowly added, The reaction was carried out at 0 ° C for 2 hours and 180 g of water was added. The mixture was stirred for 30 minutes, allowed to stand for delamination and then washed once with 100 g of water. The layers were separated and the organic layer was added with 24 g of anhydrous sodium sulfate. After drying for 1 hour and filtering, the organic phase of the reduced product was obtained. The content of the reduced product was 53.8 g, the molar yield 92.1% and the GC purity ≧ 99.0%.

[0120] (4)Halogenation reaction: the reduction product obtained in step (3) is taken as organic phase (containing 53.8 g of reduced product), 2.0 g of MDF is added, the temperature is controlled at 25-40 ° C., 36.0 g of thionyl chloride is added dropwise while keeping the temperature dropping, , The reaction 4.0 hours, the reaction system was slowly added to a 0 ~ 5 ° C aqueous solution of sodium carbonate (800g, sodium carbonate mass fraction of 8%), the layers were separated, the organic layer was added 200g water washing, standing stratification, organic Layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered to give a side chain organic phase, the content was detected, side chain 56.0g, 96% molar yield, GC purity ≧ 99.0%.

[0121] Example 3

[0122] Preparation of side chains:

[0123] (1)Condensation: 30 g of N-ethylethanolamine, 1.2 g of tetrabutylammonium bromide, 25 g of potassium hydroxide, 240 g of chloroform and 120 g of water were charged into a reaction flask, and then the temperature was controlled at 20 to 30 ° C. 38 g of 5-chloro- 2-pentanone, after the dropwise addition, the reaction was stirred for 3 hours, still stratified, the aqueous phase was discarded, the organic layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered, the filtrate is The organic phase of the condensation product was detected. The content of the condensation product was 51.7g, the molar yield was 94.7% (based on 5-chloro-2-pentanone) and the GC purity was ≧ 98.5%.

[0124] (2)Esterification reaction: the condensation product obtained in step (1) organic phase (condensation product 51.7g) was cooled to 0 ~ 5 ℃, incubated dropwise 24g acetyl chloride, after the addition was complete, the reaction was incubated for 2 hours, the reaction was completed and the reaction The solution was slowly added to an aqueous solution of sodium carbonate (350 g, mass fraction of sodium carbonate 6%) previously cooled to 0-5 ° C and stirred for 30 minutes. The layers were separated and the organic layer was washed with 200 g of water and the layers were separated. Water and sodium sulfate at a controlled temperature of 10 to 20 DEG C, stirring and drying for 1 hour and filtering to obtain an organic phase of the esterified product. The content of the esterified product was detected. The esterified product was 59.6g, the molar yield was 93.2% and the GC purity was ≧ 99.0%.

[0125] (3)Reduction reaction: 40g of ethanol was added to the organic phase (59.6g of the esterified product) of the esterified product obtained in the step (2), the temperature was lowered to -5 to 0 DEG C, 12.0g of sodium borohydride was slowly added, and the reaction was incubated 2.0 hours, 180g of water was added and stirred for 30 minutes, standing stratification, and then washed once with 100g of water, standing stratification, the organic layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered , The organic phase of the reduced product was obtained, and the content thereof was measured. The yield of the reduced product was 55.6 g, the molar yield was 92.4% and the GC purity was ≧ 99.0%.

[0126] (4)Halogenation reaction: The organic phase of the reduction product (55.6g containing the reduction product) prepared in the step (3) is added with 2.0g of MDF, the temperature is controlled at 25-40 DEG C, 36.0g of thionyl chloride is added dropwise while keeping the temperature dropping, , The reaction 4.0 hours, the reaction system was slowly added to a 0 ~ 5 ° C aqueous solution of sodium carbonate (800g, sodium carbonate mass fraction of 8%), the layers were separated, the organic layer was added 200g water washing, standing stratification, organic Layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered to give a side chain organic phase, the content was detected, side chain 57.0g, molar yield 94.5%, GC purity ≧ 99.0%.

[0127] Example 4

[0128] Preparation of side chains:

[0129] (1)Condensation reaction: 30 g of N-ethylethanolamine, 0.6 g of tetrabutylammonium bromide, 25 g of potassium hydroxide, 240 g of chloroform and 120 g of water were added to a reaction flask, and then the temperature was controlled to be 20 to 30 ° C. 38 g of 5- 2-pentanone, after completion of the dropwise addition, the reaction was stirred for 3 hours, standing stratification, the aqueous phase was discarded, the organic layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered, As the condensation product of the organic phase, the content was detected, the condensation product 50.2g, the molar yield of 91.9% (5-chloro-2-pentanone dollars), GC purity ≧ 98.5%.

[0130] (2)Esterification reaction: the condensation product obtained in step (1) organic phase (condensation product 50.2g) was cooled to 0 ~ 5 ℃, 24g acetyl chloride was added dropwise, after completion of the dropwise addition, the reaction was incubated for 2 hours, the reaction is complete, the reaction The solution was slowly cooled to 0-5 ° C in an aqueous solution of sodium carbonate (350g, mass fraction of sodium carbonate 6%) and stirred for 30 minutes. The layers were separated and the organic layer was washed with 200g of water. The layers were separated and the organic layer was added with 24g of anhydrous sulfuric acid Sodium. The temperature was controlled at 10 ~ 20 ℃. The mixture was stirred and dried for 1 hour and filtered to obtain the organic phase of the esterified product. The content of the esterified product was determined. The esterified product was 57.4g, the molar yield was 92.4% and the GC purity was ≧ 99.0%.

[0131] (3)Reduction reaction: 40g of ethanol was added to the organic phase (57.4g of the esterified product) of the esterified product obtained in the step (2), the temperature was lowered to -5 ~ 0 ℃, 12.0g of sodium borohydride was slowly added, 2.0 hours, 180g of water was added and stirred for 30 minutes, standing stratification, and then washed once with 100g of water, standing stratification, the organic layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered , The organic phase of the reduced product was obtained, and the content thereof was measured. The amount of the reduced product was 54.4 g, the molar yield was 93.8% and the GC purity was ≧ 99.0%.

[0132] (4)Halogenation reaction: The organic phase of the reduction product (54.4g containing the reduction product) prepared in the step (3) was added 2.0gMDF, the temperature was controlled at 25 ~ 40 ℃, 39.0g of thionyl chloride was added dropwise while keeping the temperature dropping, , The reaction 4.0 hours, the reaction system was slowly added to a 0 ~ 5 ° C aqueous solution of sodium carbonate (800g, sodium carbonate mass fraction of 8%), the layers were separated, the organic layer was added 200g water washing, standing stratification, organic Layer was added 24g anhydrous sodium sulfate, the temperature was controlled at 10 ~ 20 ℃, stirred and dried for 1 hour, filtered to obtain a side chain organic phase, the content was detected, side chain 56.7g, molar yield 96.1%, GC purity ≧ 99.0%.

[0133] Example 5

[0134] Preparation of hydroxychloroquine sulfate:

[0135] (A) N Protection reaction: 45 g of 4-amino-7-chloroquinoline and 5 g of DMF were added to 180 g of chloroform, and the temperature was raised to 30 to 40 ° C. 50.0 g of p-

toluenesulfonyl chloride was added and reacted for 3 hours. After the reaction was completed, The system was added to a sodium hydroxide solution (200 g, sodium hydroxide mass fraction 8%) at 0-10 ° C. The layers were separated and the organic layer was further washed with 100 g of water. The layers were separated and the organic layer was concentrated under reduced pressure to recover the chloroform. The mixture was refluxed at elevated temperature for 30 minutes, then cooled to 0-5 ° C to recrystallize, filtered, and dried at 50-60 ° C to obtain 80 g of 4-Tos amino-7-chloroquinoline, 95.5% of moles and purity of ≧ 99.5%.

[0136] (B) Condensation reaction: 78.0 g of 4-Tos amino-7-chloroquinoline obtained in the step (A), 3.0 g of tetrabutyl Ammonium bromide, and the temperature was raised to 65-70 ° C. After the reaction for 6.0 hours, the system was cooled to 20-30 ° C and added to an aqueous solution of sodium hydroxide (300 g, sodium hydroxide mass fraction 15%) at 30-40 ° C. The reaction mixture was incubated at 30-40 ° C for 6.0 hours, cooled to 10-15 ° C and allowed to stand for delamination. The organic layer was concentrated to give a crude product of hydroxyquinoline after recovering the chloroform by addition of 260 g of 95% ethanol, 10 ℃, recrystallization, filtration, dried at 50 ~ 60 ℃ hydroxyquinoline base 110.4g, the molar yield of 96.1% (4-amino-7-chloroquinoline dollars), purity ≧ 99.5%.

[0137] (C) Salt-forming reaction: Take 70g of hydroxyquinoline base prepared in step (B) and add 200g of 95% ethanol into a reaction flask, increase the temperature to 50-60 ° C, dissolve, and dropwise add 18.8g of 80% , The reaction was incubated for 1 hour after the addition was completed, cooled to 0 to 10 ° C for 2.0 hours, filtered and dried at 50-60 ° C to obtain 57.7 g hydroxychloroquine sulfate, with a molar yield of 93.2% and a purity of ≧ 99.8% %, The largest single impurity ≦ 0.1%, the unknown impurity ≦ 0.1%, the ignition residue ≦ 0.2%, the water ≦ 0.3%, and the heavy metal ≦ 10 ppm.

[0138] Example 6

[0139] Preparation of hydroxychloroquine sulfate:

[0140] (A) N Protection reaction: 45 g of 4-amino-7-chloroquinoline and 5 g of DMF were added to 180 g of chloroform, the temperature was raised to 30 to 40 ° C, 52.0 g of p-toluenesulfonyl chloride was added and reacted for 4 hours. After the reaction was completed, The system was added to a sodium hydroxide solution (200 g, sodium hydroxide mass fraction 8%) at 0-10 ° C. The layers were separated and the organic layer was further washed with 100 g of water. The layers were separated and the organic layer was concentrated under reduced pressure to recover the chloroform. The mixture was refluxed at elevated temperature for 30 minutes, then cooled to 0-5 ° C to recrystallize, filtered and dried at 50-60 ° C to obtain 81.3 g of 4-Tos amino-7-chloroquinoline, 97.02% of molar purity and ≧ 99.5% of purity.

[0141] (B) Condensation reaction: 72.0 g of 4-Tos amino-7-chloroquinoline obtained in the step (A), 2.5 g of tetrabutyl Ammonium bromide, and the temperature was raised to 65-70 ° C. After the reaction for 6.0 hours, the system was cooled to 20-30 ° C and added to an aqueous solution of sodium hydroxide (300 g, sodium hydroxide mass fraction 15%) at 30-40 ° C. The reaction was incubated at 30-40 ° C for 6.0 hours, cooled to 10-15 ° C and allowed to stand for delamination. The organic layer was concentrated and recovered to give a crude product of hydroxyquinoline based on the recovery of chloroform, followed by addition of

260 g of 95% ethanol. The mixture was warmed to 0 ~ 10 ℃, recrystallization, filtration, drying at 50 ~ 60 ℃ hydroxyquinoline 101.9g, the molar yield of 95.3% (4-amino-7-chloroquinoline dollars), purity ≧ 99.5%.

[0142] (C) Salt-forming reaction: Take 70g of hydroxyquinoline base prepared in step (B) and add 200g of 95% ethanol into a reaction flask, increase the temperature to 50-60 ° C, dissolve, and dropwise add 18.8g of 80% , The reaction was incubated for 1 hour after the addition was completed, cooled to 0 to 10 ° C for 2.0 hours, filtered and dried at 50-60 ° C to obtain 58.1 g of hydroxychloroquine sulfate with a molar yield of 93.8%, purity of ≧ 99.8% and total impurity of ≦ 0.2 %, The largest single impurity ≦ 0.1%, the unknown impurity ≦ 0.1%, the ignition residue ≦ 0.2%, the water ≦ 0.3%, and the heavy metal ≦ 10 ppm.

[0143] Example 7

[0144] Preparation of hydroxychloroquine sulfate:

[0145] (A) N Protection reaction: 45 g of 4-amino-7-chloroquinoline and 5 g of DMF were added to 180 g of chloroform, the temperature was raised to 30 to 40 ° C, 52.0 g of p-toluenesulfonyl chloride was added and reacted for 4 hours. After the reaction was completed, The system was added to a sodium hydroxide solution (200 g, sodium hydroxide mass fraction 8%) at 0-10 ° C. The layers were separated and the organic layer was further washed with 100 g of water. The layers were separated and the organic layer was concentrated under reduced pressure to recover the chloroform. The mixture was refluxed at elevated temperature for 30 minutes, then cooled to 0-5 ° C to recrystallize, filtered and dried at 50-60 ° C to obtain 80.6 g of 4-Tos amino-7-chloroquinoline, 96.19% of moles and purity of ≧ 99.5%.

[0146] (B) Condensation reaction: 72.0 g of 4-Tos amino-7-chloroquinoline obtained in the step (A), 2.5 g of tetrabutyl Ammonium bromide, and the temperature was raised to 65-70 ° C. After the reaction for 6.0 hours, the system was cooled to 20-30 ° C and added to an aqueous solution of sodium hydroxide (300 g, sodium hydroxide mass fraction 15%) at 30-40 ° C. The reaction was incubated at 30-40 ° C for 6.0 hours, cooled to 10-15 ° C and allowed to stand for delamination. The organic layer was concentrated and recovered to give a crude product of hydroxyquinoline based on the recovery of chloroform, followed by addition of 260 g of 95% ethanol. The mixture was warmed to 0 Recrystallization at -10 ° C, filtering and drying at 50-60 ° C to obtain 100.7g of hydroxyquinolyl group with a molar yield of 95.0% (based on 4-amino-7-chloroquinoline) with a purity of ≧ 99.5%.

[0147] (C) Salt-forming reaction: Take 70g of hydroxyquinoline base prepared in step (B) and add 200g of 95% ethanol into a reaction flask, increase the temperature to 50-60 ° C, dissolve, and dropwise add 18.8g of 80% , The reaction was incubated for 1 hour after the addition was completed, cooled to 0 to 10 ° C for 2.0 hours, filtered and dried at 50-60 ° C to obtain 58.7 g of hydroxychloroquine sulfate with a molar yield of 94.8% and a purity of ≧ 99.8% %, The largest single impurity ≦ 0.1%, the unknown impurity ≦ 0.1%, the ignition residue ≦ 0.2%, the water ≦ 0.3%, and the heavy metal ≦ 10 ppm.

[0148] Example 8

[0149] Preparation of hydroxychloroquine sulfate:

[0150] (A) N Protection reaction: 45 g of 4-amino-7-chloroquinoline and 5 g of DMF were added to 180 g of chloroform, the temperature was raised to 30 to 40 ° C, 52.0 g of p-toluenesulfonyl chloride was added and reacted for 4 hours. After the reaction was completed, The system was added sodium hydroxide aqueous solution (200g, sodium hydroxide mass fraction 8%) at 0-10 ° C. The layers were separated and the organic layer was further washed with 100g of water and the layers were separated. The organic layer was concentrated under reduced pressure to recover the chloroform, Methanol, and heated to reflux for 30 minutes to dissolve, cooled to 0 ~ 5 ℃ recrystallization, filtered, dried at 50 ~ 60 ℃ to obtain 80.9g 4-Tos amino-7-chloroquinoline, 96.50% molar purity ≧ 99.5%.

[0151] (B) Condensation reaction: 75.0 g of 4-Tos amino-7-chloroquinoline obtained in the step (A), 3.0 g of tetrabutyl Ammonium bromide, and the temperature was raised to 60-65 ° C. After the reaction was completed for 6.0 hours, the system was cooled to 20-30 ° C and added to an aqueous solution of sodium hydroxide (300 g, sodium hydroxide mass fraction 15%) at 30-40 ° C. The reaction was incubated at 30-40 ° C for 6.0 hours, cooled to 10-15 ° C and allowed to stand for delamination. The organic layer was concentrated and recovered to give a crude product of hydroxyquinoline based on the recovery of chloroform, followed by addition of 260 g of 95% ethanol. The mixture was warmed to 0 ~ 10 ℃ recrystallization, filtration, dried at 50 ~ 60 ℃ hydroxyquinoline 103.4g, the molar yield of 93.6% (4-amino-7-chloroquinoline dollars), purity ≧ 99.5%.

[0152] (C) Salt-forming reaction: Take 70g of hydroxyquinoline base prepared in step (B) and add 200g of 95% ethanol into a reaction flask, increase the temperature to 50-60 ° C, dissolve, and dropwise add 18.8g of 80% , The reaction was incubated for 1 hour after the addition was completed, cooled to 0 to 10 ° C for 2.0 hours, filtered and dried at 50-60 ° C to obtain 57.8 g of hydroxychloroquine sulfate with a molar yield of 93.6% and a purity of ≧ 99.8% %, The largest single impurity ≦ 0.1%, the unknown impurity ≦ 0.1%, the ignition residue ≦ 0.2%, the water ≦ 0.3%, and the heavy metal ≦ 10 ppm.

[0153] Example 9

[0154] High performance liquid chromatography (HPLC), using liquid as the mobile phase, using a high-pressure infusion system, a single solvent with different polarity or different proportions of mixed solvents, such as mobile phase buffer was pumped into the stationary phase of the column, After the components are separated in the column, enter the detector for testing, in order to achieve the analysis of the sample. The HPLC chromatogram of the hydroxychloroquine sulfate sample prepared in Example 5 is shown in FIG. 2, and the HPLC chromatogram of the hydroxychloroquine sulfate reference standard is shown in FIG. 3.

[0155] As can be clearly seen from the comparison of FIG. 2 and FIG. 3, the hydroxychloroquine sulfate prepared by the present invention has less impurity types, higher total purity and lower maximum single impurity purity than the hydroxychloroquine sulfate reference standard, and is superior in quality In the reference.

[0156] As described above, this is an embodiment of the present invention. The present invention is not limited to the above embodiments. Anyone should understand that structural changes made under the inspiration of the present invention, and any technical solutions that have the same or similarities with the present invention fall into the protection scope of the present invention.

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Method for simultaneous detection of hydroxychloroquine side chains, raw materials and intermediates by gas chromatography

[PDF]

Abstract

The invention belongs to the technical field of drug analysis and particularly relates to a method for simultaneous detection of hydroxychloroquine side chains, raw materials and intermediates by gaschromatography. The method can simultaneously determine the hydroxyl side chains, ethylamine, xylene, ethylamine ethanol, chloropentanone, ethylamine diethanolamine, amino pentanone and ethanol, and the specificity, linearity, range, precision, detection line, and accuracy are in line with the requirements of the verification guiding principles for quality standard analysis methods of traditionalChinese medicines in Chinese Pharmacopoeia 2015 Edition Volume IV. The method aims to provide a technical basis for the detection and monitoring of the synthesis process of the hydroxychloroquine sidechains.

[0001] Technical field

[0002] The invention relates to the technical field of drug analysis, in particular to a method for simultaneous detection of hydroxychloroquine side chains and their raw materials and intermediates by gas chromatography.

[0003] Background technique

[0004] Hydroxychloroquine (formula I), chemically named 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethyl-2-pentyl] aminoquinoline, is a 4-aminoquinoline Drugs, originally used clinically for the treatment of anti-Plasmodium, are now widely used in the treatment of discoid lupus erythematosus and systemic lupus erythematosus, and are also the first choice for the treatment of rheumatoid arthritis. In addition, they have immunosuppressive and anti-inflammatory reactions. Other aspects also have applications.

[0005]

[0006] Hydroxychloroquine is synthesized from 4,7-dichloroquinoline and 5-(N-ethyl-N-2-hydroxyethylamine)-2-pentylamine in a cost-synthetic reaction, among which 5-(N-ethyl) -N-2-hydroxyethylamine)-2-pentylamine (Formula II), also known as hydroxychloroquine side chain, is a key intermediate for the synthesis of hydroxychloroquine. There are seven kinds of raw materials and intermediates involved in the synthesis route of a hydroxychloroquine side chain (Formula III) disclosed in Chinese Patent (Published: CN 104803859 A), which are ethylamine (Formula 1) and xylene (Formula 1). 5) Ethylamine Ethanol (Formula 2), Chloropentene (Formula 4), Ethylamine Diethanolamine (Formula 3), and Amino Pentoxone (Formula 6). Residues of intermediates with incomplete raw materials and reactions in the reaction The high purity results in low purity of the target product and will affect the yield of hydroxychloroquine synthesized with 4,7-dichloroquinoline in the later period, thereby reducing the quality and clinical efficacy of hydroxychloroquine. Therefore, it is particularly necessary to carry out quality control during the synthesis of hydroxychloroquine side chains.

[0007]

[0008] From the structural formula of the hydroxychloroquine side chain, it is known that there is no conjugation effect and significant ultraviolet absorption, and it is generally difficult to analyze it by liquid chromatography, which is simple, convenient, and cost-effective. In addition, the raw materials and intermediates of the hydroxychloroquine side chain are all liquid and have the characteristics of small molecular weight and good thermal stability. Therefore, gas chromatography is suitable for analysis. Gas chromatography (GC) technology has the characteristics of high efficiency, convenience, and accurate separation. It has become an important research field for instrument analysis and provides an indispensable important analysis basis for the disciplines of physics, chemistry, and medicine. Today, GC is a very mature technology and its application will continue to deepen and expand.

[0009] Summary of the Invention

[0010] The object of the present invention is to provide a rapid, convenient, accurate, and sensitive method for the simultaneous detection of hydroxychloroquine side chains and the seven starting materials and intermediates involved in the process by gas chromatography.

[0011] In the present invention, by using direct injection gas chromatography, the simultaneous determination of seven kinds of raw materials involved in the hydroxychlorochloroquine side chain and its technological process was established through the selection and optimization of different stationary phases, temperature-programmed time and sample preparation solvent. The new method of the intermediates and the scientificity, accuracy and feasibility of the analytical method of the invention have been confirmed through verification, aiming to provide a technical basis for the detection and monitoring of the synthesis process of hydroxychloroquine side chains.

[0012] In order to achieve the above object of the present invention, the following technical solutions are adopted.

[0013] A gas chromatographic method for the detection of hydroxychloroquine side chains and their starting materials and intermediates. The method for the simultaneous detection of hydroxychloroquine side chains, ethylamine, ethylamine ethanol, ethylamine diethanolamine, chloropentanone, xylene, amino-pentane Ketone and ethanol; includes the following steps:

[0014] (1)Chromatographic conditions

[0015] The chromatographic column is a cross-linked capillary column, which is heated by a program; the inlet temperature is 250-310°C; the carrier gas is nitrogen; the detector is a hydrogen flame ionization detector FID, the detector temperature is 260-315°C; the hydroxychloroquine side chain Ethylamine, ethylamine, ethylamine ethanol, ethylamine diethanolamine, chloropentanone, xylene, aminopentanone, and ethanol have a resolution of greater than 1.5;

[0016] (2)Preparation of mixed control solution

[0017] The hydroxychloroquine side chain, ethylamine ethanol, xylene, chloropentanone, ethylamine diethanolamine, aminopentanone, ethylamine and ethanol were accurately weighed and placed in the same volumetric flask and diluted with a solvent to make a mixture. Reference solution; every 1 mL of the mixed reference solution, the

hydroxychloroquine side chain is 0.01 to 0.09 g, ethylamine ethanol, xylene, chloropentanone, ethylamine diethanolamine, aminopentanone, and ethanol are independently 0.001 to 0.009. g, ethylamine 0.011 ~ 0.019g;

[0018] (3)Preparation of the test solution

[0019] Take hydroxychloroquine side chain, accurately weighed, solubilized and diluted to make a uniform solution containing 0.19 ~ 0.30g of this product per 1mL as the test solution;

[0020] (4)Determination

[0021] The precise volume of the mixed reference solution and the test solution were measured and injected separately into the gas chromatograph for determination.

[0022] In the present invention, in step (1), the cross-linked capillary column is selected from any of DB-1, HP-1, HP-5 or DB-624 cross-linked capillary columns.

[0023] In the present invention, in step (1), the initial temperature of the program temperature increase is 80 to 120° C. for 1 to 8 minutes, and the temperature is increased to 180 to 240° C. at a rate of 12 to 17° C./min and stored for 3 to 15 minutes.

[0024] In the present invention, in step (1), the flow rate of nitrogen is 1.5 to 3.5 mL/min, and the split ratio is 25:1 to 35:1.

[0025] In the present invention, in step (2) and step (3), the solvent is DMF, DMSO, or N-methylpyrrolidone.

[0026] In the present invention, in step (2), the hydroxychloroquine side chain is 0.04 to 0.06 g, ethylamine ethanol, xylene, chloropentanone, ethylamine diethanolamine, amino pentanone and ethanol per 1 mL of the mixed standard solution. Independent from 0.004 to 0.006g and ethylamine 0.014 to 0.016g.

[0027] In the present invention, in step (3), a uniform solution containing 0.22 to 0.26 g of the product is used as a test solution per 1 mL.

[0028] In the present invention, in the step (4), the volume of the mixed reference solution and the test solution is 0.6 to 1 μL.

[0029] Compared with the prior art, the beneficial effects of the present invention are:

[0030] The present invention discloses the simultaneous determination of seven kinds of raw materials and intermediates including hydroxychloroquine side chain and ethanol, ethylamine ethanol, xylene, chloropentanone, ethylamine diethanolamine, amino pentane and ethylamine by gas chromatography. method.

[0031] Validated by methodology, its specificity and system adaptability, linearity, range, detection limit, precision, and accuracy meet the requirements of the Guiding Principles for Validation of Methods for the Analysis of Drug Quality Standards in the Appendix of the 2015 edition of the Chinese Pharmacopoeia.

[0032] This method provides a technical basis for the detection and monitoring of hydroxychloroquine side chain synthesis processes.

[0033] Description of the drawings

[0034] Figure 1 shows the chromatogram of the reference solution. 1. Ethylamine, 2. Ethylamine ethanol, 3. Ethylamine diethanolamine, 4. Chloropentanone, 5. Xylene, 6. Aminopentanone, 7. Etanol, II. Hydroxychloroquine side chain. 8. NMP.

[0035] Figure 2 blank solution assay chromatograms.

[0036] detailed description

[0037] The technical scheme of the present invention will be described in detail below with reference to the accompanying drawings and embodiments.

[0038] Example 1

[0039] (1)Chromatographic condition and system suitability test The column was a DB-624 cross-linked capillary column (30m×0.53mm.id, 3.0μm); the initial temperature of the program temperature was kept at 100°C for 2 minutes, and then the temperature was raised to 200°C at a rate of 15°C. Store for 10 min; injector temperature is 300°C; carrier gas is nitrogen; detector is hydrogen flame ionization detector (FID), detector temperature is 310°C; flow rate is 3.0 mL/min, split ratio is 30:1; The degree of separation of chloroquine side chain, ethylamine, ethylamine ethanol, ethylamine diethanolamine, chloropentanone, xylene, aminopentanone, and ethanol should be greater than 1.5;

[0040] (2)Preparation of Mixed Reference Solution Take ethylamine ethanol, xylene, chloropentanone, ethylamine diethanolamine, aminopentanone, ethylamine, hydroxychloroquine side chain (pure product, lot number: Y023-150101, from Shanghai Zhongxi three-dimensional drug Industry Co., Ltd.) The appropriate amount, respectively, accurately weighed, placed in the same bottle, add N-methylpyrrolidone dissolved and diluted to produce about 1mL each containing ethylamine ethanol, xylene, chloropentanone, ethylamine diethanolamine, A standard solution of 0.004 g of amino pentane, 0.016 g of ethylamine, and 0.05 g of a hydroxychloroquine side chain was used as a control solution.

[0041] (3)The test solution was prepared by taking the appropriate amount of hydroxychloroquine side chain (pure product, lot number: Y023-150101, supplied by Shanghai Zhongxi 3D Pharmaceutical Co., Ltd.), accurately weighed, and dissolved and diluted with N-methylpyrrolidone to make 1 mL each. About 0.25g of this product as a homogeneous solution for the test solution;

[0042] (4)Measure the precise amount of each of the mixed reference solution and the test solution by 1 μL. The direct injection method is injected into the gas chromatograph to determine the value.

[0043] Application example: Simultaneous determination of hydroxychloroquine side chains and their raw materials and intermediates by gas chromatography

[0044] Hydroxychloroquine is a 4-aminoquinoline drug. It was first used clinically for the

treatment of anti-parasites. It is now widely used in the treatment of discoid lupus erythematosus and systemic lupus erythematosus. It is also the first choice for the treatment of rheumatoid arthritis. . In addition, there are also applications in immunosuppressive and anti-inflammatory reactions. The hydroxychloroquine side chain is a key intermediate for the synthesis of hydroxychloroquine. There are seven kinds of raw materials and intermediates involved in the synthesis of hydroxychloroquine side chain lines. The excessive amount of raw materials and incomplete reaction intermediates in the reaction will lead to the purity of the target product is not high, and the byproduct of the reaction is cyclopropyl. The ketonic ketone is difficult to remove in the reaction of the late hydroxychloroquine side chain and 4,7-dichloroquinoline to synthesize hydroxychloroquine, thereby reducing the quality and clinical efficacy of hydroxychloroquine. Therefore, it is particularly necessary to carry out quality control during the synthesis of hydroxychloroquine side chains. After the experiment and research, the simultaneous determination of hydroxychloroquine side chain, its synthetic raw materials and the intermediates of ethylamine, ethylamine ethanol, ethylamine diethanolamine, chloropentanone, xylene, amino pentane and ethanol content were established. law.

[0045] The methodological review is as follows:

[0046] (1)Specificity and System Adaptability

[0047] Separately take the appropriate amount of hydroxychloroquine side chain, ethylamine, ethylamine ethanol, ethylamine diethanolamine, chloropentanone, xylene, aminopentanone, and ethanol to prepare a solution by dissolving N-methylpyrrolidone and carry out the headspace as described above. Samples were taken and assayed. The results showed (see Figure 1) that the retention times were 15.869 min for the hydroxychloroquine side chain, 2.531 min for ethylamine, 5.904 min for ethylamine ethanol, 11.613 min for ethylamine diethanolamine, 7.691 min for chloropentanone, Xylene 6.399, 6.497, 6.841 min, aminopentanone 16.646 min, ethanol 2.662 min.

[0048] (2)Linear

[0049] The appropriate amount of hydroxychloroquine side chain was taken and diluted with N-methylpyrrolidone to form a series of standard solutions containing hydroxychloroquine side chains of 1.0600, 3.2580, 7.6986, 19.246, 28.870, 72.174, 96.232, 120.29 mg/mL, respectively. Determine the chromatographic conditions and determine the peak area (Y) for the linear regression of the concentration of the corresponding solvent (X, mg/mL). The linear relationship of the hydroxychloroquine side chain in the concentration range of 1.06 to 120.29mg/mL is good, and the regression equation is:

[0050] Hydroxychloroquine side chain Y=304609X-887401 R2=0.9992

[0051] (3)Precision

[0052] Precisely take 2 mL of the test solution and dilute to 5 mL with solvent to obtain a solution containing 100 mg of hydroxychloroquine side chains per mL. Prepare 6 parts, according to the proposed chromatographic conditions, into the gas chromatograph, record the peak area. The relative standard deviation RSD was calculated to be 1.52%, in line with the requirements of the 2015 edition of the Chinese Pharmacopoeia.

[0053] (4)Minimum detection limit

[0054] The detection limit of the hydroxychloroquine side chain with S/N=3 was 0.2379 μg/mL.

[0055] Accuracy

[0056] Take 2mL of the test solution and dilute to 5mL with solvent to obtain a solution containing 100mg of hydroxychloroquine side chains per mL. Six parts were prepared and injected into the gas chromatograph according to the above chromatographic conditions. Area normalization method was used to calculate the average content of 6 parts was 99.42%. Another precision weighing hydroxychloroquine side chain 0.60g plus appropriate amount of glacial acetic acid dissolved. Six parts were prepared and potentiometrically titrated with a 0.1% perchloric acid titrant to calculate the content, and the average content was calculated to be 98.97%. The hydroxychloroquine side chain stock solution was taken and diluted with N-methylpyrrolidone in three concentration gradients of 80%, 100%, and 120%. Each concentration was prepared in 3 portions for a total of 9 parts. According to the above chromatographic conditions, the sample was injected into the gas phase. Chromatograph. The area normalization method calculates an average content of 99.38%. The three methods have an RSD of 0.25%

[0057] The results show that the product has good accuracy.

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HIGH-YIELDING CONTINUOUS FLOW SYNTHESIS OF ANTIMALARIAL DRUG HYDROXYCHLOROQUINE

[PDF]

Abstract

Cost effective, semi-continuous flow methods and systems for synthesizing the antimalarial drug hydroxychloroquine (HCQ) in high yield are provided. The synthesis method that uses simple, inexpensive reagents to obtain the crucial intermediate 5-(ethyl(2-hydroxyethyl)-amino)pentan-2-one, vertical-integration of the starting material 5-iodopentan-2-one and the integration of continuous stirred tank reactors.

001] HIGH-YIELDING CONTINUOUS FLOW SYNTHESIS OF ANTIMALARIAL DRUG HYDROXYCHLOROQUINE

[0003] STATEMENT OF FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0004] This invention was made with government support under contract W91 INF- 16-2-0023 awarded by the Defense Advanced Research Projects Agency (DARPA). The United States government has certain rights in the invention.

[0005] BACKGROUND OF THE INVENTION

[0006] Field of the Invention

[0007] The invention generally relates to improved, cost effective, semi-continuous flow systems and methods for synthesizing hydroxychloroquine (HCQ). In particular, the invention provides a synthesis method that uses simple, inexpensive reagents to obtain the crucial intermediate 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one, vertical-integration of the starting material 5-iodopentan-2-one, and the integration of continuous stirred tank reactors (CSTRs).

[0008] Description of Related Art

[0009] In 2016, an estimated 212 million cases of malaria, including 429,000 fatalities, were reported worldwide, with the majority of these cases occurring in sub-Saharan Africa and Southern Asia. The malaria epidemic is particularly difficult to control due to the multi-drug resistant nature of the malaria parasite Plasmodium falciparum.

[0010] Hydroxychloroquine (Figure 1A, HCQ) is an anti-malarial drug developed for both treatment and prevention of the disease in response to the widespread malaria resistance to chloroquine, (Figure IB, CQ). The World Health Organization has identified HCQ as an essential anti-malarial medication for a basic healthcare system. Additionally,

[0011] hydroxychloroquine (HCQ) is an effective non-steroidal anti-inflammatory drug in the treatment of various autoimmune diseases such as rheumatoid arthritis (e.g. in cardiovascular patients), lupus, and childhood arthritis (or juvenile idiopathic arthritis) among others.

[0012] Unfortunately, global access to HCQ has been hindered by high manufacturing costs. Thus, the development of cost effective synthetic strategies to increase global access to this important global health drug is of great importance. The current HCQ commercial synthesis employs the key intermediate 5-(ethyl(2-hydroxyethyl) amino)pentan-2-one, 6, and its production is a major cost driver (see Figure 2A). An alternative route (Figure 2B) by Li and co-workers (2015) eliminates the protection-deprotection steps, but its use of a complex multi transition metal catalyst system to achieve direct SN 2 substitution of the chlorine on 3 by the amine 7, is sub-optimal.

[0013] There is a pressing need to develop new methods of synthesizing HCQ that are cost effective while producing the drug in high yield.

[0014] SUMMARY OF THE INVENTION

[0015] Other features and advantages of the present invention will be set forth in the description of invention that follows, and in part will be apparent from the description or may be learned by practice of the invention. The invention will be realized and attained by the compositions and methods particularly pointed out in the written description and claims hereof.

[0016] Provided herein is a cost effective semi-continuous flow method for the synthesis of the antimalarial drug HCQ. The synthesis involves the reaction of simple, inexpensive reagents to obtain crucial intermediates for the reaction, and overall employs a reduced number of synthesis steps while achieving a high, multi gram yield of the product. The synthetic strategy involves vertical-integration of the starting material 5-iodopentan-2-one and the integration of continuous stirred tank reactors for key steps of the method.

[0017] It is an object of this invention to provide a method for synthesizing

[0018] hydroxychloroquine (HCQ), comprising: in a flow reactor, i) reacting 5-iodopentan-2-one with 2-(ethylamino)ethan-l-ol to form 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one; and ii) converting 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one to

[0019] (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime; and in a first continuous stirred tank reactor (CSTR) iii) contacting (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime with a catalyst to form 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane; and in a second CSTR. iv) reacting the 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane with 4,7,-dichloroquinoline in the presence of a base to form HCQ. In some aspects, steps i), ii) and iii) are conducted in a solvent that is the same for each step. In additional aspects, the solvent is tetrahydrofuran (THF). In other aspects, reacting step iv) is performed in an alcohol. In further aspects, the alcohol is ethanol. In yet further aspects, the base is K^CCL/EtsN. In other aspects, reacting step iv) proceeds for 6 hours. In additional aspects, the 5-iodopentan-2-one is formed by a) reacting a-acetyl butyrolactone with an iodine donor in an aqueous solvent. In yet further aspects, the method further comprises a step of b) extracting the 5-iodopentan-2-one from the aqueous solvent with an organic solvent. In additional aspects, the steps of a) reacting and b) extracting are performed in line in a first flow reactor. In other aspects, the first flow reactor is in line with the flow reactor of claim 1. In further aspects, the iodine donor is hydroiodic (HI) acid. In yet further aspects, the a-acetyl butyrolactone is neat. In additional aspects, the step of extracting is performed using a hydrophobic, membrane-based separator. In further aspects, the catalyst is a Raney nickel catalyst.

[0020] The disclosure also provides a system for synthesizing hydroxychloroquine (HCQ), comprising a first heated reactor coil configured to receive 5-iodopentan-2-one and

[0021] 2-(ethylamino)ethan-l-ol and output 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one; a first packed bed reactor comprising a neutralizing agent and configured to receive

[0022] 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one from the first heated reactor and output neutralized 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one; a second heated reactor coil configured to receive neutralized 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one from the first packed bed reactor, receive hydroxylamine, and output (E)-5-(ethyl(2-hydroxyethyl) amino)pentan-2-one oxime; a second packed bed reactor comprising a neutralizing agent and configured to receive 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime from the second heated reactor coil, and output neutralized (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime; a first continuous stirred tank reactor (CSTR) configured to contain a catalyst, receive neutralized (E)-5-(ethyl(2-hydroxyethyl)amino) pentan-2-one oxime from the second packed bed reactor, and output 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane; and a second CSTR configured to receive 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane from the first CSTR, receive 4,7,-dichloroquinoline, and output HCQ. In certain aspects, the system further comprises a heated reaction coil configured to receive a-acetyl butyrolactone and receive an iodine donor, and output 5-iodopentan-2-one, a reaction coil configured to receive

[0023] 5-iodopentan-2-one from the heated reaction coil, and receive a base and a hydrophobic, membrane-based separator configured to receive 5-iodopentan-2-one from the unheated reaction coil extract 5-iodopentan-2-one from the aqueous solvent with an organic solvent, and output 5-iodopentan-2-one in an organic phase. In additional aspects, the first heated reactor coil receives the 5-iodopentan-2-one in an organic phase from the

hydrophobic, membrane-based separator. In yet further aspects, the catalyst is a Raney nickel catalyst. BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1A and B. Commercially available antimalarial drugs. A, hydroxychloroquine (HCQ); B, chloroquine (CQ).

[0025] Figure 2A and B. Batch Syntheses of 5-(ethyl(2-hydroxyethyl) amino)pentan-2-one. A, prior art method; B, prior art method of Li (2015).

[0026] Figure 3. Retrosynthetic strategy to hydroxychloroquine.

[0027] Figure 4. Flow process for synthesis of 5-iodopentan-2-one (10).

[0028] Figure 5. Schematic representation for continuous in-line extraction of 10.

[0029] Figure 6. Schematic representation of continuous telescoped process to synthesize 11.

[0030] Figure 7. Schematic representation of reductive amination of 12.

[0031] Figure 8. Optimization of the flow process for synthesis of 12.

[0032] Figure 9. Schematic representation of a flow system.

[0033] Figure 10. 'H NMR Spectra of compound (10).

[0034] Figure 11.I3 C NMR Spectra of compound (10).

[0035] DETAILED DESCRIPTION

[0036] Provided herein is a highly efficient method for the semi-continuous synthesis of the antimalarial drug hydroxychloroquine (HCQ). The method is“semi-continuous” because some steps of the method are conducted using continuous flow but others are conducted using continuous stirred tank reactors (CSTR) which are vertically integrated into the process. The method results in an overall yield improvement of about 52% over the current commercial HCQ production process, even though the methods use reactants that are simpler and less expensive than those employed in current commercial processes. A key feature in the new process is the elimination of protecting groups without invoking the use of expensive catalysts as required by Li (2015). The present high-yielding, multigram-scale semi-continuous synthesis thus provides an opportunity to achieve increased affordable global access to hydroxychloroquine for the prevention and treatment of malaria and various autoimmune diseases.

[0037] The reactions of the continuous flow method are preferably carried out using the same solvent for several steps; however, this is not necessarily always the case. Those of skill in the art may choose to separate one or more of the optimized steps of the method and/or to use a different solvent or multiple solvents (e.g. rinsing the lines with the appropriate solvent prior to use), to make HCQ. Alternatively, one or more of the optimized reactions, either individually or in groups of several reactions, may be used for purposes other than making HCQ. For example, the starting materials and intermediates described herein are useful chemicals for a variety of purposes, and may be of interest in and of themselves, without

further conversion. All such methods of making each chemical entity disclosed herein are encompassed.

[0038] DEFINITIONS

[0039] Raney nickel catalyst: Raney nickel is a fine-grained solid composed mostly of nickel derived from a nickel-aluminum alloy. Several grades are known, but most are gray solids. Some are pyrophoric, most are used as air-stable slurries. The original form, Raney®-Nickel is a registered trademark of W. R. Grace and Company, but other generic forms are known and are also referred to generically as“Raney nickel” or as e.g. "skeletal catalyst" or

[0040] "sponge-metal catalyst". These catalysts have properties similar to those of Raney®-Nickel. The catalyst may be a binary Ni-Al alloy and/or may comprise small amounts of a third metal (a "promoter") such as zinc or chromium, forming a ternary alloy. The third metal enhances the activity of the catalyst. All forms of this catalyst may be used in the methods described herein. Continuous stirred-tank reactors (CSTR), also known as vat- or backmix reactors, or continuous-flow stirred-tank reactors (CFSTR), are known in the art. CSTRs facilitate rapid dilution rates which make them resistant to both high pH and low pH fluctuations. It is sometimes economically beneficial to operate several CSTRs in series, e.g. for the same reaction, and this strategy may be implemented in the present methods. This allows, for example, the first CSTR to operate at a higher reagent concentration and therefore a higher reaction rate. In these cases, the sizes of the reactors may be varied in order to minimize the total capital investment required to implement the process.

[0041] Room temperature generally refers to a temperature of from about 15 - 25 °C, and is generally about 20-22 °C.

[0042] REACTIONS

[0043] Synthesis of starting material (10)

[0044] In the present synthesis, 5-iodopentan-2-one (10) replaces the traditional chlorinated starting material (3 in Figure 2). This iodinated starting material is made using a-acetyl butyrolactone 8 (used neat) via a decarboxylative ring-opening reaction, generally via reaction with an aqueous solution of an iodine donor (e.g. see Figure 4). Iodine donors that may be used include but are not limited to e.g. HI, FI, Nal, KI, Lil, etc. In some aspects, the iodine donor is HI in an aqueous solution. The amount of iodine donor (e.g. Hl) is typically at least about 20 to about 60%, and is generally at least about 40%, and is preferably at least about 50%, such as about 55%. The temperature of the reaction is generally at least about 40 °C or above, e.g. about 40, 45, 50, 55, 60, 65, 70, 75, 80, 85 or 90 °C, with about 80 °C being a preferred temperature. The reaction optimally proceeds for about 2.5 to about 15 minutes, e.g. about 2.5, 5.0, 10.0, or 15.0 minutes or longer, with about 5-10 minutes being the preferred range, e.g. about 5, 6, 7, 8, 9, or 10 minutes. The reaction pressure is generally from about 1.5 to 5.0 bar, e.g. about 1.5, 2.0, 3.0, 3.5, 4.0, 4.5 or 5.0 bar, with about 3 bar being preferred.

[0045] The reaction can optionally be monitored, e.g. by GC-MS, 'H NMR, etc. No intermediates are produced and the starting material is completely consumed during the reaction.

[0046] In preferred aspects, extraction and neutralization are accomplished in-line as part of a flow-based method as shown in Figure 5. An amphoteric compound which functions as a base (such as saturated sodium bicarbonate (NaHC03) or Na3 C03 , (sodium carbonate), potassium carbonate (K2 CO3), etc.,) and one or more suitable organic solvents (e.g. hexanes and/or methyl tert- butyl ether, methylene chloride (DCM), ethyl acetate, etc.) are introduced in-line and are reacted with 5-iodopentan-2-one (10) in a reactor coil maintained at room temperature (e.g. about 25 °C). One or more hydrophobic, membrane-based separators receive the input from the reactor coil and it is used to produce an aqueous waste stream (comprising excess HI) and an organic stream comprising 10. Examples of suitable hydrophobic,

[0047] membrane-based separators include but are not limited to: Zaiput, Versapore®, Zefluor™, polytetrafluoroethylene (PTFE), polycarbonate membrane, etc. When a membrane-based separator is used, there is a loss of product to the water layer (e.g. generally 10% or less) but this is tolerated in order to avoid the need for complete batch workup steps.

[0048] In some aspects, 10 is then transferred (integrated) directly into a flow method, e.g. as the input to the next reactor coil, depicted in Figure 6. Alternatively, the reaction and separation may be done in batch in which crude 10 is extracted (generally at room

[0049] temperature) e.g. with one or more hydrophobic solvents (as listed above), and neutralized e.g. to about pH = 7 using a base (as listed above). The combined organic phases are dried (e.g. using anhydrous sodium sulfate) and evaporated in vacuo to dryness to yield 10 for use in the first step of the semi-continuous synthesis method described in detail below.

[0050] STEPS OF THE REACTION TO FORM HCQ

[0051] Synthesis of 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (6):

[0052] 5-iodopentan-2-one (10) formed as described above is used to synthesize

[0053] 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (6) as follows:

[0054] Compound 6 is synthesized from 10 in a flow reactor unit, preferably using a solvent system that is compatible with subsequent flow reactions of the method. In some aspects, the solvent is tetrahydrofuran (THF). However, other solvents such as 1,4-dioxane, 2-methyl THF (tetrahydrofuran), MTBE (methyl tert-butyl ether), DCM (dichloromethane or methylene chloride), etc., may also be employed. Those of skill in the art will recognize the advantages of rinsing the flow reactor with dry solvent and/or flushing the system with an inert gas (e.g. N2) prior to use.

[0055] To perform the reaction, 10 is combined with 2-(ethylamino)ethan-l-ol (7) in a suitable solvent, e.g. THF at about room temperature and streamed into a reactor coil, as depicted in Figure 6. The temperature in the coil is in the range of from about 70 to 90 °C, e.g. about 70, 95, 80, 85 or 90 °C, and the flow rate typically ranges from about 0.1 to about 1.0 ml/min, e.g. about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 ml/min or higher, for larger coils.

[0056] The reaction is then quenched by passing the reaction mixture e.g. through a packed bed reactor containing e.g. potassium carbonate, sodium carbonate, lithium carbonate, lithium

hydroxide, sodium bicarbonate, or other suitable material. The temperature in the packed bed reactor is generally about 85 - 100 °C, such as about 85, 90, 95 or 100 °C. This yields product 6, which is transferred directly to the next in-line step.

[0057] Alternatively, the output of the reaction between 10 and 7 is collected and quenched, extracted with one or more organic solvents (e.g. DCM) and the combined organic layers are dried over sodium sulfate, and evaporated to give 6, which can be used in further reactions. Synthesis of (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime (11)

[0058] Compound 6 is ultimately converted to 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane 12 via intermediate oxime 11. Briefly, a simple conversion of the ketone group of 6 yields oxime 11, which is then reduced to give 12.

[0059] A. Synthesis of oxime 11

[0060] The conversion of 6 to oxime 1 1 is preferably done in-line as part of a continuous flow synthesis method, as shown in Figure 6. 6 is combined with an agent such as NfTOFl (e.g. about 0.5, 1.0 or 1.5 M). This reaction is generally performed in a reactor coil (e.g. at about 0.5, 1.0 or 1.5 mF/min, such as about 1.0 mF/min) at a temperature of from about 80 to 100 °C, e.g. about 80, 85, 90, 95 or 100 °C, and with a tR of about 15-30 minutes, e.g. about 15,

[0061] 20, 25, or 30 minutes such as about 20 min. The reaction is quenched e.g. by passage through a packed bed reactor comprising a compound such as potassium carbonate, sodium carbonate, lithium carbonate, lithium hydroxide, sodium bicarbonate, etc. The temperature in the packed bed reactor is generally about 85 - 100 °C, such as about 85, 90, 95 or 100 °C. This yields oxime 11. If needed, 11 is e.g. concentrated, taken up in a solvent such as DCM, etc. prior to the next reaction. However, further purification is generally not needed and 11 may pass directly to the next step.

[0062] Synthesis of 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane (12)

[0063] The next to last step of the production of HCQ is the conversion of oxime 11 to 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane (12). Accordingly, product 11 is passed to the next reaction, which takes place in a continuous stirred tank reactor (CSTR). 11 is efficiently reduced to 12 in a CSTR using a suitable solvent (e.g. THF, diglyme, 1,4-dioxane, methanol, ethanol, 2-methyl THF, IPA (2-propanol)), etc. Significantly, the reaction proceeds in the presence of a Raney Nickel catalyst, which is retained or sequestered in the CSTR. The reaction mixture comprises compound 11 at a concentration ranging from about 0.05-2.0 M (such as about 0.05. 0.1. 0.2. 0.3. 0.4. 0.5. 0.6, 0.7. 0.8. 0.9, 1.0. 1.1 , 1.2. 1.3. 1.4. 1.5. 1.6. 1.7, 1 .8. 1.9. or 2.0. in a suitable solvent. The solvent is preferably the same as that which is used in the prev ious How steps, such as THF or diglyme, 1 ,4-dioxane, methanol, ethanol, 2-methyl THF, IPA. etc. However, this is not strictly necessary and methods w hich use other solvents for one or more steps of the method are also encompassed. The reaction mixture is generally introduced into the reaction vessel at a set Ho rate of e.g. 0.6-2.5 mL min1 such as about 0.6, 1 .0, 1.5, 2.0 or 2.5 mL min1 . The reaction pressure is typically set to about 5- 15 bar. such as about 10 bar with an inert gas such as hydrogen supplied at a suitable How rate (e.g. 0.1 to 1 .0 mL min 1 , such as about 0.5 mL min1). The reaction takes place at a temperature in the range of from about 70 to about 90 °C. e.g. about 70, 75. 80, 85 or 90 °C. such as about 80 C. The reaction generally proceeds w ith agitation e.g. stirring (e.g. at about

500 to 100 rpm. such as about 750 rpm) to provide proper mixing. The reaction volume may be monitored and hen suitable (e.g. hen a difference between two thermocouples is detected, such as about a 1. 2, 3. 4. or 5 °C difference, such as a 3°C difference) a level control opens allow ing products to exit the reactor. Conversely, when the temperature difference between the two thermocouples is greater than e.g. about 1. 2. 3. 4, or 5 °C. such as 3°C. reactants enter the tank. Product is collected e.g. when a steady-state is reached. The reaction mixture is

[0064] (optionally) filtered and/or dried, extracted , etc., prior to being used in the next (and last) step of the reaction.

[0065] Synthesis of hydroxychloroquine (1)

[0066] The final step in the synthesis of HCQ involves the reaction of 12 with 4,7,-dichloroquinoline, 13. This step is also performed in a CSTR, and the reactions take place in an alcohol solvent, preferably ethanol. However, in some aspects, other alcohols such as methanol, n-butanol, isopropanol, etc. may be employed. The reactants are 12 plus a suitable base, e.g. NaOH, KOH, K2 CO3 , ET3 N, D1PEA (N,N-Diisopropylethylamine), or combinations thereof, especially combinations with ET3 N such as NaOH/ETiN, DIPEA/ET3 N or K2 CO3 /ET3 N. In preferred aspects, K2 C03 /Et3 N is used. This step is advantageously accelerated (compared to conventional methods) by employing K2 CC>3 /Et3 N. As a result, a high yield of HCQ is obtained, e.g. in less than about 6 hours of reaction time.

[0067] Reactants, 13 and 12 are combined in approximately a 1/1 molar ratio (e.g. about 1/1.2 molar ratio, respectively) with equal equivalents of Et3N and K2 CO3 . The amount of each of Et3 N and K2 C03 is generally about half that that of reactant 13, mole/mole. The reactants are combined in sufficient solvent e.g. ethanol to allow thorough mixing. The reaction is allowed to proceed in an inert atmosphere (e.g. under N2) at a temperature of about 100 to 150 °C, e.g. at about 100, 105, 1 10, 1 15, 120, 125, 130, 135, 140, 145 or 150 °C, such as about 125 °C, and requires about 6 hours for completion.

[0068] Following completion of the reaction, ethanol is removed (e.g. via distillation) and the product is recovered e.g. by extraction, separation, drying, etc. as needed to afford the final product.

[0069] SYSTEMS

[0070] Also provided are systems for synthesizing hydroxychloroquine (HCQ) . The systems are semi-continuous flow systems and comprise elements/components that are in-line, flow components and also CSTRs. For example, the systems generally comprise a plurality of reaction coils (also referred to herein as“reactor coils”), e.g. generally 3 or 4, which may or may not be heated, depending on the reaction(s) that take place within a coil. The systems also generally comprise a plurality of packed bed reactors. In addition, various lines, valves, connectors, separators, reservoirs (e.g. to serve as sources of a reactant), etc. are included in the system, and the system components are advantageously operably linked in-line. That is to say, generally a product, such as a reactant, that is produced in one component of the system is transferred directly to a component in which it undergoes a further reaction, without intervening steps of purification (other than e.g. steps of phase separation, neutralization, etc. which can also be done in-line).

[0071] In some aspects, the systems comprise a first heated reactor coil that is configured to (i.e. comprises a least one inlet to) receive 5-iodopentan-2-one and 2-(ethylamino)ethan-l-ol, and an outlet to output 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one, usually directly into a first packed bed reactor. The first packed bed reactor typically comprises a neutralizing agent and is configured to include an inlet to receive input from first heated reactor coil, typically 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one. The 5-(ethyl(2-hydroxyethyl)amino) pentan-2-one flows through the first packed bed reactor, is neutralized, and is then passed directly to a second heated reactor coil configured to (having at least one inlet to) receive neutralized 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one from the first packed bed reactor. The second heated coil is also configured to receive hydroxylamine, and a reaction takes place in the second heated coil to form (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime.

[0072] The oxime is output from the second heated reaction coil to a second packed bed reactor, which like the first packed bed reactor, comprises a neutralizing agent. The neutralizing agents in the first and second packed bed reactors may be the same or different. The second packed bed reactor comprises an inlet to receive 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime from the second heated reactor coil and and outlet to output neutralized

[0073] (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime.

[0074] The systems disclosed herein also comprise one or more continuous stirred tank reactors (CSTRs) which comprise a stirring mechanism. For example, a first CSTR is generally configured to contain a Raney nickel catalyst, receive neutralized

[0075] (E)-5-(ethyl(2-hydroxyethyl)amino) pentan-2-one oxime from the second packed bed reactor, and output 5-(ethyI(2-hydroxyethyl)amino)-2- aminopentane. This CSTR generally also comprises an inlet for a gas, e.g. an iert gas such as FT. Typically the output of the first CSTR is received by a second CSTR. The second CSTR receives both

[0076] 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane (from the first CSTR) and

[0077] 4,7,-dichloroquinoline (from a source of 4,7,-dichloroquinoline). The reaction between these two chemicals within the second CSTR produces HCQ, which can subsequently be output from the second CSTR for further processing, if needed (e.g. via extraction, purification, concentration, drying, etc. Further processing generally also includes forming the HCQ into dosage forms, e.g. tablets, liquid dosage forms, etc.

[0078] Is some aspects, the 5-iodopentan-2-one that is input into the first reaction coil is transferred from another in-line flow system, which may be integrated directly into the system described above, or may be a stand-alone system. This second system comprises at least a heated reaction coil configured to receive a-acetyl butyrolactone and an iodine donor. The reaction that takes place in the heated reaction coil produces 5-iodopentan-2-one, which is then output to a reaction coil configured to receive the 5-iodopentan-2-one from the heated reaction coil, and also to receive a base. The reaction coil may or may not be heated because the reaction takes place, e.g. at room temperature (rt). However, in some aspects, heating may be required to maintain the reaction coil at a consistent temperature, e.g. at or near rt. This segment of the overall system further comprises at least one hydrophobic, membrane-based separator with an inlet to receive 5-iodopentan-2-one from the rt reaction coil. The hydrophobic, membrane-based separator extracts 5-iodopentan-2-one into an organic solvent,

and outputs the 5-iodopentan-2-one in an organic phase via a suitable outlet. In some aspects, the 5-iodopentan-2-one is transferred directly in-line into the first heated reactor coil described above, e.g. without intervening steps of collection, purification, etc. In other aspects, the 5-iodopentan-2-one is collected and processed as needed, before being provided as the starting material in the semi-continuous system described above, e.g. before being input into the first reaction coil.

[0079] A schematic, non-limiting representation of an exemplary semi-continuous flow system is shown in Figure 9. Depicted are multiple reaction coils 110, 111, 112 and 113; multiple reservoirs (120, 121, 122, 123 and 124) for containing/storing reactants which are supplied to other components via connecting lines (170), valves (not depicted), etc., a hydrophobic membrane separator 130 from which waste passes through waste line 135 to waste container 136, multiple bed reactors 140 and 141, two CSTRs 150 and 151, and a gas storage tank 160. In the exemplary system that is shown:

[0080] reactants a-acetyl butyrolactone (8) and an iodine donor flow from reservoirs 120 and 121, respectively;

[0081] starting material 5-iodopentan-2-one (10) is produced in reaction coil 110 and flows to reaction coil 111 as do e.g. hexane/MTBE and NaHC03 (from reservoirs 122 and 123, respectively);

[0082] 5-iodopentan-2-one (10) and the reaction milieu enter hydrophobic membrane separator 130; 5-iodopentan-2-one (10) in an organic phase flows from membrane separator 130 to reaction coil 12 while aqueous waste flows to waste container 136 via waste line 135;

[0083] 2-(ethylamino)ethan-l-ol (7) is introduced to reaction coil 112 from reservoir 124;

[0084] 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (6) is produced in reaction coil 112 and enters packed bed reactor 140, where the reaction is quenched;

[0085] 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (6) enters reaction coil 113 together with a base from reservoir 125;

[0086] (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime (11) is produced in reaction coil 113 and then passes through packed bed reactor 141 and then to CSTR 150;

[0087] 5-(ethyl(2-hydroxyethyl)amino)-2-aminopentane (12) is synthesized in CSTR 150 (e.g.

[0088] containing Raney nickel catalyst 80 and under FF gas from gas storage tank 160) and passes to CSTR 151; and 4,7,-dichloroquinoline, 13 enters CSTR from reservoir 126, and the final product, HCQ is synthesized in CSTR 116.

[0089] The arrow leaving CSTR 151 illustrates removal of HCQ.

[0090] It is to be understood that this invention is not limited to particular embodiments described herein above and below, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0091] Where a range of values is provided, it is understood that each intervening value between the upper and lower limit of that range (to a tenth of the unit of the lower limit) is included in the range and encompassed within the invention, unless the context or description clearly dictates otherwise. In addition, smaller ranges between any two values in the range are encompassed, unless the context or description clearly indicates otherwise.

[0092] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Representative illustrative methods and materials are herein described; methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention.

[0093] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference, and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual dates of public availability and may need to be independently confirmed.

[0094] It is noted that, as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as support for the recitation in the claims of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitations, such as "wherein [a particular feature or element] is absent", or "except for [a particular feature or element]", or "wherein [a particular feature or element] is not present (included, etc.)...".

[0095] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

[0096] EXAMPLE

[0097] The continuous synthesis described herein involves a retrosynthetic process (Figure 3) in which 10, an iodo analogue to starting material 3, is generated in a single step via a decarboxylative ring-opening of a-acetyl butyrolactone 8. The iodo-analogue, 10, is then used without isolation to prepare compound 6.

[0098] A direct one-step reductive animation of 6 to give 12 can be accomplished by simple heterogeneous reduction with H2 /Raney-Nickel. However, THF is employed in all of the prior flow steps and is a poor choice as a solvent for the reductive amination step due to limited solubility of ammonia in THF. H2/Raney-Nickel reductions are often carried out in alcoholic media where much higher concentrations of ammonia are achievable but would

require a solvent exchange. There are many reports of continuous flow chemistry methods for reductive amination of ketones [25-31]; however, such processes typically require soluble reductants such as diisobutylaluminium hydride (DIBAL-H), superhydrides, or supported borohydride species [32-36] Although these approaches are effective, they are significantly more costly than using simple heterogeneous reduction with H2/Raney-Nickel. Therefore, we explored an alternate strategy: first, simple conversion of the ketone group of 6 to oxime 11, which is then followed by reduction with H2 /Raney-Nickel to give 5-(ethyl(2-hydroxyethyl)amino)- 2-aminopentane 12. This efficiently reduces 11 to 12 with THF as the solvent in a continuous stirred tank reactor (CSTR).

[0099] The last step of HCQ synthesis requires reaction of 12 with 4,7,-dichloroquinoline, 13, which when used neat takes 24-48 hours at 120-140°C to give 75-80% yield of HCQ, 1 [37]. We have found that this step can be accelerated by employing K2 C03/ triethylamine, to facilitate the formation of HCQ, 1, resulting in a comparable yield in less than 6 hours. Thus, we have integrated the continuous preparation of reaction with a new efficient continuous flow synthesis of 12 with the final step by using a CSTR to accommodate the longer reaction time required to produce HCQ. Initial optimization efforts to prepare 6 revealed poor reactivity of starting material 3, so we pursued the iodo-analogue of 3, 5-iodopentan-2-one (10) as an alternative. By optimizing the reaction concentration, we have also shown that 10 reacts rapidly and cleanly with 7 under flow conditions to give 6 in high-yield (>80%). Furthermore, we have developed and optimized a continuous synthesis of 10 (Table 1, (Figure 4), wherein hydroiodic acid is reacted with neat 3-acetyldihydrofuran-2(3H)-one, 8, to provide a rapid route to 10 which is significantly higher in yield than previously reported syntheses [38-39] Initial results using diluted hydroiodic acid (20-40%) provided only modest conversion to product over a range of temperatures (Table 1, entries 1-5); however, use of 55% hydroiodic acid (Table 1, entries 6-8) was found to give near quantitative conversion. The reaction profile was monitored using GC-MS and 'H NMR - no intermediates were observed under these conditions. Optimization of the flow rate with 55% hydroiodic acid (Table 1, entries 6-8) revealed that a flow rate of 1.0 ml min1 (/«= 5 min) gave an isolated yield of 89%.

[0100] Table 1. Optimization of the Flow Process for Synthesis of 10

[0101] Entry HI Temp (°C) tR =min Pressure Conv ^ (%)

[0102] [Aqueous%] (bar)

[0103] 1 20 r.t. 5 1.5 5

[0104] 2 20 40 5 2.0 31

[0105] 3 20 80 5 2.0 34

[0106] 4 40 80 5 2.0 43

[0107] 5 40 80 5 2.5 46

[0108] 6 55 80 5 3.0 98 (89%)b

[0109] 7 55 80 2.5 3.0 91

[0110] 8 55 80 10 3.0 92

[0111] [a] conversion determined by GC-MS and Ή NMR [b] Isolated yield

[0112] Due to the need to use an excess of hydroiodic acid it is important to remove its excess from the eluting reaction stream before telescoping into the next step in flow. The product stream containing crude 10 was mixed in-line with methyl-tertbutylether (MTBE) and saturated NaHCC>3 before phase separation using a hydrophobic, membrane-based separator (Zaiput) [40] (Scheme 3) to afford purified 10 in the organic phase. A loss of 5-10% of product to the water layer was observed, however this was deemed adequate as it prevented the need for a complete workup step in batch.

[0113] In the next step, 6 was reacted with hydroxylamine, which was facilitated by passing through a packed-bed of K2 CO3 to give oxime 11 (Table 2). As was seen with the reaction to produce 6 (Table 1) reactant concentrations also had a dramatic effect on oxime formation. A series of experiments were conducted to optimize the continuous formation of 11. Reaction yields were modest at lower reactant concentrations across several temperatures and residence times (Table 2). Conversion to 11 increased when reactant concentrations were increased (9% at 0.1 M to 72% at 1 M) (Table 2, entries 1-6). Optimization of the flow rate with 1 M concentrations of each reactant (Table 2, entries 6-8) showed that a flow rate of 1.0 ml min1 (/«= 20 min) was optimal, giving an isolated yield of 78% (Table 2, entry 7).

[0114] Table 2. Optimization of conversion of 6 to oxime 11

[0115] Entry Concentration^ Temp (°C) tR =min Conv of l l

[0116] o/„]

[0117] 1 0.1 M 100 10 9

[0118] 2 0.2 M 100 10 16

[0119] 3 0.4 M 100 10 34

[0120] 4 0.6 M 100 10 37

[0121] 5 0.8 M 100 10 62

[0122] 6 1.0 M 100 10 72 7 1.0 M 100 20 85 (78)tc]

[0123] 8 1.0 M 100 40 76 [a] Concentration of 10, 7 and hydroxylamine; [b] conversion determined by GC-MS and 'H NMR; [c] Isolated yield

[0124] The reductive amination of 11 performed in the first generation batch process was carried out using Raney Nickel at 80 °C, 10 bar hydrogen pressure for 4-6h [21-24]. In order to perform this step in a continuous fashion, a continuous stirred tank reactor [25, 41] was employed (Table 3). Materials were delivered to the CSTR vessel through an HPLC pump and reacted under hydrogen pressure with mechanical stirring. The dip tube in the CSTR was outfitted with a fritted metal filter, allowing for retention of the heterogeneous catalyst within the CSTR vessel. Optimization of this CSTR-based flow process (Table 3) showed near

quantitative yields of 12 over a broad range of oxime 11 reactant concentrations. An optimum residence time was determined to be hours.

[0125] Table 3. Optimization of synthesis of 12

[0126] Entry Oxime Temp (°C) Pressure tR = hours Conv of l2

[0127] [Concentration] (bar) (%)[a]

[0128] 1 0.05 M 80 10 4 94%

[0129]

[0130] [a] conversion determined by GC-MS and H NMR [b] Isolated yield

[0131] After optimizing the individual steps up to compound 12 the entire reaction was telescoped into a continuous reaction process that converts 10 and 6 into 12 (Figure 8) with an overall isolated yield of 68% for compound 12.

[0132] With an optimized continuous process for producing the key intermediate 12, in-hand, reaction conditions for the conversion of 12 to HCQ were examined. In the commercial process this step is carried in batch under neat reactant conditions and requires a relatively long reaction time of 24-48h [42-44] In order to convert this step to a flow chemistry method, we employed a CSTR (Table 4). This final step, transforming 12 and 13 into 1, was first investigated in batch to optimize the conditions when implemented in an CSTR.

[0133] Table 4: Optimization of hydroxychloroquine 1

[0134]

[0135] Entry Base Solvent Temp Conv. to 1

[0136] (°C) (%)[a]

[0137] 1 NaOH EtOH 125 30

[0138] 2 KOH EtOH 125 35

[0139] 3 K2 C03 EtOH 125 82

[0140] 4 Et3 N EtOH 125 61

[0141] 5 DIPEA EtOH 125 55

[0142] 6 K2 C03 /Et3 N EtOH 125 88 (78)b

[0143] Reaction condition: 4,7-Dichloroquine 13 (1.0 equiv.), base (1.0 equiv.), amine 12 (1.2 equiv) [a] conversion determined by HPLC and 'H NMR [b] Isolated yield

[0144] Process optimization for the final step began by screening the effect of solvent and

base(s) on HCQ yield. Screening of different polar-protic and non-protic solvents (see Table S-2 in SI) [45] demonstrated that ethanol is most effective for this transformation. During the screening of bases, the pKa of the amine and alcohol groups present in compound 12 were given careful consideration in order to minimize C-0 bond formation (Table 4). NaOH or KOH in ethanol gave low (<40%) conversion, whereas using K2 C03 in ethanol gave 82% conversion to HCQ (Table 4, Entry 3). Attempts with organic bases (Entries 5-6) resulted in only moderate conversions to the desired product; however, using a 1 :1 mixture of K2 C03 /Et3 N (1/1) in ethanol resulted in 88% conversion (Table 4, Entry 6) to 1, with corresponds to an isolated yield of 78%.

[0145] Conclusion

[0146] In summary, we have developed a high-yielding continuous flow process for the synthesis of hydroxychloroquine (HCQ) by optimizing continuous flow methods for the synthesis of key intermediates 6 and 12. Additionally we have developed and optimized flow chemistry conditions for performing reductive animation of 1 1 using Raney-Nickel as catalyst in a continuous stirring tank reactor (CSTR) for the synthesis of compound 12, and have incorporated it into a fully continuous telescoped process for synthesis of 12 from lactone 8 and aminoethanol 7. Feeding the output stream containing 12 from the above CSTR into a second CSTR in which 12 is converted to HCQ provides a completely continuous flow process from producing HCQ from readily available starting materials. This efficient process has the potential to increase global access to this strategically important antimalarial drug.
Optimization Reactions

[0147] All reactions for the preparation of substrates performed in standard, dry glassware under an inert atmosphere of nitrogen or argon unless otherwise described. All starting materials and reagents purchased from commercial sources and used as received unless otherwise noted.! H and13 C NMR spectra recorded using 600 MHz spectrometers. Chemical shifts (d) values given in ppm, and coupling constants (J) given in Hz. The 7.26 resonance of residual CHCft (or 0 ppm of TMS) for proton spectra and the 77.23 ppm resonance of CDCI3 for carbon spectra were used as internal references. Continuous flow experiments were carried out using the E-series flow reactor instrument purchased from Vapourtec Ltd. PFA tubing (1/16 OD x 1 mm ID) was used for all reactor coils in flow experiments. Most of the reagents and starting materials were purchased from commercial sources and used as received. All HPLC chromatograms recorded on Agilent Technologies 1260 Infinity instrument with a Poroshell 120 EC-C18 column (4.6 x 50 mm, 2.7 micron). Continuous flow hydrogenation was performed using FlowCAT instrument. Synthesis of 5-iodopentan-2-one (10):

[0148] Two solutions, 2-Acetylbutyrolactone (8) (1.176 mL, 10.35 mmol, 1.0 equiv) and Hydroiodic acid (55% aqueous sol) were pumped at 1.0 mLmin1 using peristaltic pumps through a 10 mL coil (residence time, tR = 5 mins) at 80 °C. The completion of the reaction was monitored using GC-MS. Complete consumption of starting material was observed. The reaction mixture was cooled to room temperature and sodium bicarbonate was added until neutralized at pH = 7. The crude mixture was extracted with hexanes/MTBE and the combined organic phases were dried over anhydrous sodium sulfate and evaporated in vacuo to dryness yielding the desired product as a light brown liquid (14.72 g, 89%).

[0149] ‘H NMR (600 MHz, CDC13): d 3.22 (t, J= 6.9 Hz, 2H), 2.59 (t, J= 6.9 Hz, 2H), 2.17

(s, 3H), 2.06 (quin, J = 7.0 Hz, 2H);, 3 C NMR (125 MHz, CDC13): d 207.4, 44.0, 30.3, 27.2, 6.7; Spectra were obtained in accordance with those previously reported [3]; see Figure 10 and Figure 1 1.

[0150] Synthesis of 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (6):

[0151] Telescope of compound 6: Prior to the start of the experiment, the flow reactor unit was rinsed with dry THF and flushed with nitrogen gas. At room temperature, the stock solutions of 5-iodopentan-2-one

[0152] (10) (1.0 M) and 2-(ethylamino)ethan-l-ol (7) in THF solution (1.0 M) were streamed in at 0.5 mLmin1 via a T-piece into a 10 mL reactor coil (tR =10 min) and passed through a packed bed reactor of potassium carbonate at 100 °C. The output solution was collected and quenched with a saturated solution of ammonium chloride. The aqueous phase was extracted by DCM (3 x 50 mL) and the organic layers were combined, dried over sodium sulfate, and evaporated in vacuo to give a light brown liquid (14.05 g, 86%);

[0153] 'H NMR (600 MHz, CDC13): d 3.53 (t, J= 5.2 Hz, 2H), 2.58 (m, 3H), 2.53 (m, 2H), 2.45 (t, J= 6.7 Hz, 4H), 2.59 (t, J= 6.9 Hz, 2H), 2.17 (s, 3H), 2.07 (quin, J= 7.0 Hz, 2H);13 C NMR (125 MHz, CDCI3): d 208.9, 58.6, 55.0, 52.4, 47.2, 41.3, 30.0, 21.2, 1 1.7;

[0154] Spectra were obtained in accordance with those previously reported [38,39]

[0155] Synthesis of (E)-5-(ethyl(2-hydroxyethyl)amino)pentan-2-one oxime (11):

[0156] Flow: Prior to the start of the experiment, the flow reactor unit was rinsed with dry THF and flushed with nitrogen gas. At room temperature, the stock solutions of 5-iodopentan-2-one (10) (1.0 M)

[0157] and 2-(ethylamino)ethan-l-ol (7) in THF solution (1.0 M) were streamed in at 0.5 mLmin1 via a T-piece into a 10 mL reactor coil (tR =10 min) and passed through a packed bed reactor of potassium carbonate. The output solution was streamlined with hydroxylamine (1.0 M) at 1.0 mLmin1 via a T-piece into a 10 mL reactor coil (tR =10 min) and passed through a packed bed reactor of potassium carbonate at 100 °C. The reaction mixture was then concentrated in vacuo, taken up in dichloromethane (3x20 mL) and concentrated under reduced pressure to yield 11 as light brown liquid. The crude product was used in the next step without further purification.

[0158] Synthesis of 2-((4-aminopentyl)(ethyl)amino)ethan-l-ol (12):

[0159] Flow: The synthesis of compound 12 was performed in a HEL continuous stirred tank reactor (CSTR) with a reaction volume of 150
mL. The reaction vessel was first charged with Raney Nickel (I .Og). The Raney Nickel catalyst was retained in the CSTR by the 2 pm metal filter frit on the diptube of the exit stream. The reaction mixture, consisting of compound 11 (0.05-2.0 M) in THF, was pumped by an HPLC pump set at a flow rate of 0.6-2.5 mLmin1 into the reaction vessel. The reaction pressure was set to 10 bar of hydrogen supplied by hydrogen gas (ultra high purity) at a flow rate of 0.5 mLmin1 . The reaction temperature was set to SO which was controlled by a thermocouple positioned in the reaction mixture. The reaction was stirred with mechanical stirring (750 rpm) to provide proper mixing. Two thermocouples were used to control the

reaction volume in the reactor by setting a level control of -3°C. The lower thermocouple constantly measured and controlled the reaction temperature and the upper thermocouple measured the temperature at approximately 150 mL reactor volume. When the two thermocouples were w ithin 3°C, the level control Opened" the exit stream diptube to allow products to exit the reactor, or closed' the exit stream diptube to allow the reactor to fill when the temperature difference between the two thermocouples was greater than 3°C. Product was collected after a full reaction volume of material (150 mL) had passed through the CSTR indicating that steady-state was reached. The reaction was monitored by liquid chromatography and 'H NMR. The reaction mixture was filtered through a celite pad and dried under reduced pressure. The solution was extracted with water (10 mL) and dichloromethane (3 x 20 mL). The organic layers were combined, washed with brine and dried over sodium sulfate and evaporated in vacuo. The resulting oil was fractionally distilled to give a colorless liquid (16.83 g, 84%). *H NMR (600 MHz, CDC13): d 3.53 (t, J =5.3 Hz, 2H), 2.89 (sx, 7 = 6.4 Hz, 1H), 2.57 (t, J= 5.5 Hz, 2H), 2.55 (t, J = 7.0 Hz, 2H), 2.45 (t, 7 = 7.0 Hz, 2H), 1.55-1.44 (m, 2H), 1.36-1.27 (m, 2H), 1.22 (t, 7= 7.1 Hz, 2H), 1.07 (d, 7 = 7.1 Hz, 2H), 1.00 (t, 7 = 7.1 Hz, 2H);l 3 C NMR (125 MHz, CDC13): d 58.2, 54.9, 53.2, 46.9, 46.7, 36.6, 23.8, 22.4, 10.6; Spectra were obtained in accordance with those previously reported [38,39]

[0160] Synthesis of 2-((4-((7-chloroquinoIm-4-yI)amino)pentyl)(ethyl)amino)ethan-l-oI (1):

[0161] Batch: In a CSTR reactor, 4,7-Dichloroquinoline (200 mg, 1.0 mmol), compound (12) (208 mg, 1.2 mmol), triethylamine (0.069 mL, 0.5 mmol, 0.5 equiv) and potassium carbonate (69 mg, 0.5 mmol, 0.5 equiv) were combined and to this mixture was added ethanol (1.0 mL). The ethanol was distilled off from the reaction
mixture and kept under nitrogen atmosphere (15 psi). The reaction was left at 125 °C in the nitrogen atmosphere for 6h. After cooling, the mixture was transferred into a separatory funnel using 1 M aqueous sodium hydroxide (5 mL) and dichloromethane (2x20mL). The organic phases were separated and the aqueous phase was re-extracted with dichloromethane (2x10 mL). The organic layers were combined and dried over sodium sulfate and evaporated in vacuo. The crude material was purified using flash chromatography with DCM:Et3 N:MeOH (95:3:2) to give a white solid (0.263 g, 78%). 'H NMR (600 MHz, CDC13): S 8.48 (d, =5.4 Hz, 1H), 7.93 (d, J =5.4 Hz, 1H), 7.70 (d, J =

[0162] 9.2 Hz, 1H), 7.34 (dd, J= 8.8, 7.3 Hz, 1 H), 6.39 (d, J=5.4 Hz, 1H), 4.96 (d, .7=7.5 Hz, 1H), 3.70 (sx, J = 6.8 Hz, 1H), 3.55 (m, 2H), 2.57 (m, 5H), 2.49 (m, 2H), 1.74-1.62 (m, 1H), 1.65-1.53 (m, 3H), 1.31 (d, J = 6.9 Hz, 3H), 1.24 (d, J = 7.2 Hz, 2H);13 C NMR (125 MHz, CDCI3): d 152.2, 149.5, 149.2, 135.0, 129.0, 125.4, 121.2, 1 17.4, 99.4, 58.6, 54.9, 53.18, 48.5, 47.9, 34.5, 24.1, 20.6, 1 1.9;

[0163] Spectra were obtained in accordance with those previously reported [38,39].

[0164] While the invention has been described in terms of its several exemplary

[0165] embodiments, those skilled in the art will recognize that the invention can be practiced with modification within the spirit and scope of the appended claims. Accordingly, the present invention should not be limited to the embodiments as described above, but should further include all modifications and equivalents thereof within the spirit and scope of the description provided herein.

CN105693606A
Asymmetric synthesis method of optically pure (R)/(S)-hydroxychloroquine
[PDF]

Abstract
The invention discloses an asymmetric synthesis method of optically pure (R)/(S)-hydroxychloroquine. 4-amino-7-chloroquinoline and 5- ethyl(2-hydroxyethyl) amine-2-pentanone are taken as starting raw materials and are subjected to an asymmetric reductive ammoniation reaction under the catalysis of chiral acid, optically pure hydroxychloroquine is obtained, and the spatial configuration of a product is controlled through spatial configuration of the chiral acid. The method adopts simple steps, the raw materials are easy to obtain, the yield is higher, the stereoselectivity is good, the operation is simple, the chiral construction cost is relatively lower, and the method is suitable for large-scale production.

[0001] Technical field

[0002] The invention belongs to the field of drug synthesis and organic synthesis, and relates to an asymmetric synthesis method of optically pure (R)/(S)-hydroxychloroquine.

[0003] Background technique

[0004] Hydroxychloroquine, chemical name 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol, has a chiral carbon center with (-)- (R)-Hydroxychloroquine and (+)-(S)-hydroxychloroquine are two optical isomers belonging to 4-aminoquinoline. The clinical use is (R)/(S) two optical isomers. The mixture is mixed in equal proportions, that is, the racemic compound is administered. It was first used in the treatment of antimalarial, hydroxychloroquine phosphate and sulfate are now widely used in the clinical treatment of discoid lupus erythematosus and systemic lupus erythematosus; in addition, hydroxychloroquine also has applications in immunosuppression and anti-inflammatory reactions. .

[0005] Recent studies have shown that hydroxychloroquine is also expected to develop into a new class of anti-diabetic drugs. In a clinical trial, 32 healthy subjects, in a double-blind, randomized trial of up to 14 weeks, showed that hydroxychloroquine can effectively increase insulin sensitivity, increase beta-cell viability, and regulate sugar Metabolism, which in turn lowers the level of HbA1c, is expected to be developed as a drug for diabetes prevention.

[0006] At the same time, studies on hydroxychloroquine metabolism in humans showed significant differences in the absorption, distribution, metabolism and excretion of (-)-(R)-hydroxychloroquine and (+)-(S)-hydroxychloroquine. The plasma protein binding rate of (-)-(R)-hydroxychloroquine was 37%, and the plasma protein binding rate of (+)-(S)-hydroxychloroquine was 64%; when the racemic compound was administered, (-) The blood concentration of -(R)-hydroxychloroquine is always higher than (+)-(S)-hydroxychloroquine, and the ratio is different in animals and humans. In addition, the metabolic constants of the optical isomers have different half-life, peak time, and drug-time curve area. More critically, the renal clearance rate of (-)-(R)-hydroxychloroquine was only about 40% of (+)-(S)-hydroxychloroquine. The enormous physiological and biochemical properties of the two isomers in the human body prompted a deeper study of the differences between (R)/(S)-hydroxychloroquine; at the same time, according to the national new drug declaration

requirements, different optical isomers should be Treat according to different chemical entities. Therefore, the development of a new optical pure hydroxychloroquine synthesis method has a positive significance for the application of this class of drugs in new fields.

[0007] The chemical synthesis of hydroxychloroquine has been studied earlier and the route is mature, but it is limited to the synthesis of racemates, and there are few synthetic methods for (R) or (S)-hydroxychloroquine. Using 5-(N-ethyl-N-2-hydroxyethylamine)-2-pentylamine as starting material, multiple resolution and recrystallization of (+)-(S)-mandelic acid can be obtained. (R) and (S)-5-(N-ethyl-N-2-hydroxyethylamine)-2-pentylamine in 55% yield; then reacted with 4,7-dichloroquinoline to give hydroxy Chloroquine. The synthetic method has a complicated route and complicated operation. Therefore, the synthesis and synthesis of new optically pure hydroxychloroquine is not only a requirement of medicinal chemistry, but also a requirement of organic chemistry.

[0008] Summary of the invention

[0009] It is an object of the present invention to provide an asymmetric synthesis of optically pure (R)/(S)-hydroxychloroquine.

[0010] In order to achieve the above object, the present invention adopts the following technical solutions:

[0011] 1)The borane reducing agent and the chiral acid are added to the organic solvent, and then uniformly stirred at room temperature (10 to 30 minutes, the solution is clarified or uniformly suspended) to obtain a mixture A, and 4-amino-7- is added to the mixture A. Chloroquinoline and 5-ethyl(2-hydroxyethyl)amine-2-pentanone (known chemical CAS: 74509-79-8) are reacted at room temperature for 1-2 h, then warmed to reflux and kept at 12~ 48h, after the reflux is completed, it is naturally cooled to room temperature to obtain a mixed solution B; the borane-based reducing agent is used in an amount of 1 to 2 times that of 4-amino-7-chloroquinoline, the chiral acid, based on the amount of the substance. The amount of use is 0.1 to 0.3 times that of 4-amino-7-chloroquinoline, and the amount of the 5-ethyl(2-hydroxyethyl)amine-2-pentanone is 1 to 4 of 4-amino-7-chloroquinoline. 2 times; the chiral acid is chiral carbonic acid, phosphoric acid or sulfonic acid;

[0012] 2)Saturated brine was added to the mixture B, extracted with ethyl acetate, and then purified by column chromatography.

[0013] The borane reducing agent is selected from the group consisting of an alkali metal borohydride, a cyano or triacetoxy substituent of the alkali metal borohydride, a borane, a borane trimethylamine complex or a tetrabutylcyano boron. Ammonium alkylate.

[0014] The alkali metal borohydride is selected from the group consisting of lithium borohydride, sodium borohydride or potassium borohydride.

[0015] The chiral acid is selected from (D) or (L)-mandelic acid, (D) or (L)-tartaric acid, (D) or (L)-di-p-methylbenzoyltartaric acid, (D) or (L)-malic acid, (D) or (L)-camphorsulfonic acid or (+) or (-)-binaphthol phosphate.

[0016] The organic solvent is selected from the group consisting of dichloromethane, tetrahydrofuran, toluene, dioxane, dimethylformamide or dimethyl sulfoxide.

[0017] The organic solvent is used in an amount such that the concentration of 4-amino-7-chloroquinoline reaches 0.1 to 1 mol/L (the concentration of the reactant has a certain influence on the yield and the optical purity, and the concentration range is a summary of the experimental results).

[0018] In the column chromatography, the packing of the chromatography column is silica gel, and the amount of the silica gel in the chromatography column is 5-20 times the mass of 4-amino-7-chloroquinoline.

[0019] The column chromatography was performed with isocratic elution. The eluent was a mixture of dichloromethane, methanol and triethylamine, and the volume ratio of dichloromethane:methanol:triethylamine=95:3:2.

[0020] The product is (-)-(R)-hydroxychloroquine and (+)-(S)-hydroxychloroquine.

[0021] The beneficial effects of the present invention are embodied in:

[0022] Compared with the prior art, the present invention uses 4-amino-7-chloroquinoline and 5-ethyl(2-hydroxyethyl)amine-2-pentanone as raw materials, and borane compound as reducing agent, chiral acid. Providing an asymmetric catalytic environment, the optically pure hydroxychloroquine is synthesized in one step by asymmetric reductive amination reaction. The stereo configuration of the chiral acid controls the stereo configuration of the product, avoiding the resolution of the racemic compound, and has a short synthetic route. The ratio and selectivity are high, the operation is simple, the chiral secondary amine construction cost is relatively low, and the environment is friendly, which is suitable for the technical advantage of large-scale synthesis.

[0023] The reducing agent used in the present invention is a borane compound, and the reducing ability is moderate and the price is low, so that the asymmetric reduction reaction has higher yield and is suitable for industrial synthesis.

[0024] Detailed ways

[0025] The invention will now be described in detail in connection with the embodiments.

[0026] Hydroxychloroquine contains a chiral carbon center, and its different optical isomers have different pharmacological and pharmacological properties. According to the national new drug declaration requirements, different optical isomers should be treated according to different chemical entities. Therefore, The construction of a chiral center is very important for the application of this class of compounds in the field of new drugs.

[0027] Example 1

[0028] Reaction process: Add 500 mL of dioxane, 3.3 g (0.15 mol) of lithium borohydride (reducing agent) and 3.5 g (0.015 mol) of (D)-camphor to a 500 mL three-necked flask equipped with a constant pressure funnel and a reflux condenser. The sulfonic acid (chiral reagent) was stirred at room temperature for 10 min to obtain a mixture. To a constant pressure funnel was added 17.8 g (0.1 mol) of 4-amino-7-chloroquinoline and 15.7 g (0.12 mol) of 5-ethyl (2- Hydroxyethyl)amine-2-pentanone and 100 mL of dioxane (solvent), and slowly drip the mixture into the mixture (about 30 min) from a constant pressure funnel.

After the completion of the dropwise addition, the reaction was continued at room temperature for 2 h, and then the temperature was raised to reflux. 110 ° C), and maintained for 12 h (TLC detection reaction). After the reaction was completed, it was naturally cooled to room temperature, 400 mL of saturated brine was added to the reaction system, and then extracted with ethyl acetate, 150 mL each time, and extracted three times. The extracted organic phase was dried over anhydrous sodium sulfate, dried and then sp. The solvent was removed by evaporation (vacuum degree 10 KPa, operating temperature 50 ° C), and then added to a silica gel column containing 150 g of silica gel (200-300 mesh) to eluent (dichloromethane:methanol:triethylamine volume ratio=95 :3:2) Isocratic elution, TLC detection, after combining the same effluent, the solvent was removed by rotary evaporation (vacuum degree 10 KPa, operating temperature 50 ° C) to obtain pale yellow liquid (+)-(S)-hydroxychloroquine (Formula 1) , product) 18.5 g, yield 55%.

[0029]

[0030] Product treatment: a small amount of product is dissolved in acetone, adding 2 times the amount of phosphoric acid, overnight reaction, suction filtration, acetone washing, drying to obtain hydroxychloroquine phosphate (phosphate is more stable, easy to operate; phosphate optical rotation parameters and other parameters have been There are reports in the literature, which is convenient for comparison).

[0031] The hydroxychloroquine phosphate was enantioselectively analyzed by chiral HPLC, ee% = 78%, [α] 20D = +79.1 ° (phosphate, c = 0.96, H2O). ESI-MS: 336 (M+H), 1H NMR (CDCl3 300 MHz) δ ppm: 0.97-0.99 (3H, t); 1.26-1.29 (3H, d); 1.44-1.80 (4H, m); 2.33-2.73 (6H, m); 3.40-3.91 (3H, m); 5.15 (1H, brs); 6.35 (1H, d); 7.26 (1H, dd); 7.73 (1H, d); 7.93 (1H, d); 8.49 (1H) , d). 13 C NMR (CDCl 375 MHz) δ ppm: 11.4; 20.2; 23.7; 34.2; 47.4; 48.1; 53.1; 54.8; 58.4; 99.1; 117.3; 121.2; 124.9; 128.5; 134.6; 149.0; Consistent with the literature report.

[0032] Example 2

[0033] The reaction process and product treatment were similar to those in Example 1, except that the solvent, reducing agent and chiral reagent were: 250 mL of toluene (150 mL in a three-necked flask, 100 mL in a constant pressure funnel), and 11 g (0.14 mol) of cyanide. Potassium borohydride and 1.89 g (0.014 mol) of (D)-malic acid. 4-Amino-7-chloroquinoline and 5-ethyl(2-hydroxyethyl)amine-2-pentanone were slowly dropped from a constant pressure funnel into a mixture of a reducing agent and a chiral reagent, and then allowed to react at room temperature for 1 h. The temperature in the reflux was 130 ° C and was maintained for 24 h.

[0034] The product was (+)-(S)-hydroxychloroquine 15.1 g, yield 45%; enantioselective chiral HPLC analysis, ee%=70%, [α]20D=+74.3° (phosphate, c= 0.94, H2O).

[0035] Example 3

[0036] The reaction process and product treatment were similar to those in Example 1, except that the solvent, reducing agent and chiral reagent were: 280 mL of dimethyl sulfoxide (180 mL in a three-necked flask, 100 mL of a constant pressure funnel), and 34 g (0.16 mol). Sodium triacetoxyborohydride and 2.4 g (0.016 mol) of (D)-mandelic acid. The temperature in the reflux was 160 ° C and held for 12 h.

[0037] The product was (+)-(S)-hydroxychloroquine 13.5 g in 40% yield. Enantioselective chiral HPLC analysis, ee% = 69%, [α] 20D = +74 ° (phosphate, c = 1.0, H 2 O).

[0038] Example 4

[0039] The reaction process and product treatment were similar to those in Example 1, except that the solvent, reducing agent and chiral reagent were: 200 mL of tetrahydrofuran (100 mL in a three-necked flask, 100 mL in a constant pressure funnel), and 140 mL of borane (0.14 mol). A tetrahydrofuran solution (1.0 M, the solvent may also be diethyl ether or dimethyl sulfide) and 4.2 g (0.028 mol) of (D)-tartaric acid. The temperature in the reflux was 80 ° C and was maintained for 48 h.

[0040] The product was (1)-(S)-hydroxychloroquine 13.9 g, yield 43%. Enantioselective chiral HPLC analysis, ee% = 88%, [α] 20D = +95.7 ° (phosphate, c = 1.02, H2O).

[0041] Example 5

[0042] The reaction process and product treatment were similar to those in Example 1, except that the solvent, reducing agent and chiral reagent were: 240 mL of dichloromethane (140 mL in a three-necked flask, 100 mL in a constant pressure funnel), and 10.2 g (0.14). Mol) borane trimethylamine complex and 2.1 g (0.014 mol) of (L)-mandelic acid. The temperature in the reflux was 75 ° C and held for 40 h.

[0043] The product was a pale brown solid, (-)-(R)-hydroxychloroquine (formula 2) 16.8 g, yield 50%.

[0044]

[0045] Enantioselective chiral HPLC analysis, ee% = 80%, [α] 20D = -82.8 ° (phosphate, c = 1.06, H2O).

[0046] Example 6

[0047] The reaction process and product treatment were similar to those in Example 1, except that the solvent, reducing agent and chiral reagent were: 160 mL of dimethylformamide (100 mL in a three-necked flask, 60 mL in a constant pressure funnel), 45.1 g. (0.16 mol) tetrabutylcyanoborohydride ammonium and 5.97 g (0.02 mol) of (+)-binaphthol phosphate. The temperature in the reflux was 150 ° C and maintained for 18 h.

[0048] The product was (+)-(S)-hydroxychloroquine 13.1 g in 39% yield. Enantioselective chiral HPLC analysis, ee% = 66%, [α] 20D = +70.1 ° (phosphate, c = 0.98, H2O).

CN103772277
Hydroxychloroquine linolenate and synthesis method thereof
[PDF]

Abstract
The invention discloses a structural formula of hydroxychloroquine linolenate and also

provides a method for preparing hydroxychloroquine linolenate. The method comprises the following steps: preparing hydroxychloroquine from hydroxychloroquine sulfate and a sodium hydroxide liquid, and purifying by adding ethyl acetate; adding an organic solvent, a catalyst and a dewatering agent in linolenic acid, then adding the prepared hydroxychloroquine to carry out constant-temperature reaction for 12-24 hours, wherein the mole equivalence ratio of linolenic acid to hydroxychloroquine is (1:1)-(1:1.5); and finally, carrying out column chromatography separation to obtain high-purity hydroxychloroquine linolenate. After lots of hydroxychloroquine linolenate is absorbed by tumor cells, hydroxychloroquine linolenate is metabolized to form hydroxychloroquine, thereby increasing the concentration of focus medicine and reducing medicine dose.

[0001] Technical field

[0002] The present invention relates to hydroxychloroquinelinone and a process for the preparation thereof.

[0003] Background technique

[0004] Hydroxychloroquine is a 4-aminoquinoline derivative which is commonly used clinically. Hydroxychloroquine is a traditional antimalarial drug used to control the clinical symptoms of malaria and the preventive prevention of malaria, rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus, and skin lesions caused or exacerbated by sunlight. . Studies in recent years have shown that hydroxychloroquine has a good inhibitory effect on a variety of malignant tumors. Hydroxychloroquine inhibits the growth of human breast cancer cells MCF-7 and MDA-MB-231 and regulates the protein acetylation process of tumor cell MCF-7. Hydroxychloroquine also inhibits the activity of chronic lymphocytic leukemia cells by inducing apoptosis in cells by activating caspase-3 and regulating the ratio of BCL-2 to Bax. Hydroxychloroquine also increases lysosomal and mitochondrial permeability, thereby inducing apoptosis. As an autophagy inhibitor, hydroxychloroquine inhibits the growth of tumor cells by inhibiting the autophagy of tumor cells, destroying the metabolism of tumor cells.

[0005] The amount of polyunsaturated fatty acids in tumor cells is much higher than that in normal cells. As an unsaturated fatty acid, alpha linolenic acid can be efficiently taken up by tumor tissues. Comprehensive application of the principle of tumor targeting prodrug design and the principle of structural splicing, designing and synthesizing prodrugs is a method for the synthesis of new drugs. The present invention synthesizes a prodrug of hydroxychloroquine (hydroxyl) by structural modification of hydroxychloroquine. Chloroquine linoleate), which utilizes the property of linolenic acid to be efficiently taken up by tumor cells, is loaded with an antitumor drug such as hydroxychloroquine to increase the drug concentration of the target site of the drug molecule, thereby achieving the purpose of improving the antitumor efficiency of the drug.

[0006] In order to solve the above-mentioned deficiencies in the prior art, the present invention proposes a new solution.

[0007] Summary of the invention

[0008] It is an object of the present invention to provide a tumor-targeted prodrug: hydroxychloroquinolinate which, after in vivo metabolism, can be a drug which reduces the

amount of a drug, reduces toxicity, and enhances antitumor activity.

[0009] At the same time, the present invention also provides a process for preparing hydroxychloroquine linolenate.

[0010] In order to achieve the above object, the technical solution adopted by the present invention is:

[0011] The invention has the structure of the hydroxychloroquinolinate prepared by using hydroxychloroquine sulfate and linolenic acid as raw materials, and the structural formula is as follows:

[0012]

[0013] The synthetic route is:

[0014]

[0015] The preparation process includes:

[0016] 1、Hydroxychloroquine is prepared by using hydroxychloroquine sulfate and sodium hydroxide solution, wherein the molar ratio of hydroxychloroquine sulfate to sodium hydroxide solution is 1:3, and then ethyl acetate is added for purification;

[0017] 2、The linolenic acid is mixed with an organic solvent, a catalyst and a dehydrating agent, and stirred under nitrogen for 5 minutes to 1 hour, and then heated to normal temperature; then the prepared hydroxychloroquine is added, and the reaction is carried out at room temperature for 12~. 24 hours, wherein the molar equivalent ratio of linolenic acid and hydroxychloroquine is 1:1 to 1:1.5;

[0018] 3、After the reaction is stopped, the organic solvent is added, and the solution is heated to 50 ° C, and washed with a hydrochloric acid solution, a saturated sodium chloride solution and water, and the organic phase is washed with anhydrous sodium sulfate and concentrated to give a brownish oil.

[0019] The oil is dissolved in methyl tert-butyl ether, and the solution is washed with hydrochloric acid solution. The oil phase is separated and dissolved in methanol. The activated carbon is decolorized and concentrated to give a yellow oil. The yellow oil is separated by column chromatography. After elution separation, it was concentrated again and dried to give hydroxychloroquinoline linoleate.

[0020] Linolenic acid requires the addition of an organic solvent, a catalyst and a dehydrating agent before it is reacted with hydroxychloroquine. Wherein the organic solvent is selected from the group consisting of chloroform, dichloromethane or ethyl acetate; the catalyst is selected from the group consisting of 4-dimethylaminopyridine, 4-methylmorpholine, triethylamine, pyridine or 1-hydroxybenzotriazole; the dehydrating agent is selected from Dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

[0021] In the preparation of hydroxychloroquinelinone, when the mixture is subjected to

column chromatography, it is necessary to select a suitable stationary phase and eluent. According to the physicochemical properties and experimental demonstration of hydroxychloroquinolinone, the stationary phase selected by the present invention is silica gel, wherein the silica gel column chromatography with 200-300 mesh has good effect, and the silica gel with 200 mesh is optimized. The eluent for column chromatography is chloroform-methanol or dichloromethane-methanol, and dichloromethane-methanol is optimally selected.

[0022] The hydroxychloroquinolinone prepared by the present invention is a novel compound which can be used to prepare an antitumor drug according to the principle of a prodrug.

[0023] In summary, the present invention has the following advantages:

[0024] Hydroxychloroquinelinone is a conjugate of hydroxychloroquine and linolenic acid through an ester bond. As a prodrug, hydroxychloroquinolinone in the body can be more effectively concentrated in the tumor site under the action of linolenic acid. Increase the concentration of hydroxychloroquine at the tumor site, reduce the accumulation of hydroxychloroquine in non-target tissues, and reduce the toxic side effects of the drug;

[0025] The esterification reaction synthesis method adopted by the invention has the advantages of simple operation, mature technology, simple post-treatment, good application prospect, and high purity chlorochloroquinolinate obtained by column chromatography.

[0026] Detailed ways

[0027] The improved hydroxychloroquinolinate of the present invention has the structural formula of Formula I and has the chemical formula C 36 H 54 O 2 N 3 Cl.

[0028] Hydroxychloroquinelinone is a new compound, which has not been reported in the literature. Its structure was confirmed by mass spectrometry MS and nuclear magnetic resonance HNMR. The data are as follows:

[0029] MS, m/z (%): 543 (M+, 5.56), 438 (M+-C6H4NO, 5.05), 333 (M+-2C6H4NO, 2.40), 106 (C6H4NO+, 100.00), 78 (C5H4N+, 48.64)

[0030] 1HNMR (CDCl3, 300MHz): δ (ppm)

[0031] 0.86(t, J = 7.5 Hz, 3H, CH3), 0.97 (t, J = 7.5 Hz, 3H, CH3), 1.26-1.44 (m, 19H), 2.03-2.12 (m, 5H), 2.34 (t, J = 7.5 Hz, 2H, COCH 2), 2.80 (t, J = 5.4 Hz, 3H), 3.16 (bs, 3H), 3.29 (bs, 2H), 3.29 (s, 2H), 3.93 (bs, 1H), 4.50 (s, 2H), 5.35-5.37 (m, 6H, CH=CH), 6.57 (bs, 1H, NH), 7.44 (s, 1H), 8.19 (s, 1H), 9.19 (bs, 2H).

[0032] Example 1

[0033] 21.7 g of 50 ml of hydroxychloroquine sulfate was weighed and placed in a 500 mL three-neck round bottom flask. Under ice bath conditions, 150 mL of water was added and stirred to dissolve. 150 mmol of 50 mL of 12% aqueous sodium hydroxide solution was slowly added dropwise, and a white oil was formed during the dropwise addition, and 50 mL of ethyl acetate was added at this time. After slowly warming to room temperature, 100 mL of ethyl acetate was added, and the organic phase was separated; the aqueous phase was extracted twice with ethyl acetate, and the organic phase was combined. The organic phase

was washed with a saturated aqueous solution of sodium chloride and water, dried over anhydrous sodium sulfate, filtered, and evaporated to give hydroxy chloroquine 16.5 g of 48.8 mmol of colorless transparent oil.

[0034] Under cooling with nitrogen and ice bath, add 32.5 mmol of a-linolenic acid 12.9 g and 220 mL of dichloromethane with a purity of 70% to a 500 mL three-neck round bottom flask, and then add an appropriate amount of 4-methylmorpholine, 4 -Dimethylaminopyridine and 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride, the reaction was allowed to warm to room temperature after stirring for 30 min. Wherein dichloromethane can be replaced by chloroform, the catalyst can be replaced by triethylamine, pyridine or 1-hydroxybenzotriazole; the dehydrating agent can use dicyclohexylcarbodiimide, N, N'-diisopropylcarbamate The imine or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride is substituted.

[0035] 48.5 mmol of hydroxychloroquine 16.5 g was added to linolenic acid, and the reaction was stirred for 12 hours. To the flask, 100 mL of methylene chloride was added, and the mixture was heated to a temperature of about 50 ° C. The mixture was washed with a hydrochloric acid solution, a saturated aqueous sodium chloride solution and purified water. Add 300 mL of methyl tert-butyl ether to the brownish yellow oil and transfer to a separatory funnel. The solution is washed with 200 mL of hydrochloric acid solution. The separatory funnel is divided into three phases, and the upper layer is methyl tert-butyl ether phase. The middle layer is oily and the lower layer is water phase. The oil was separated and dissolved in 200 mL of methanol. EtOAc was evaporated. The column chromatography was carried out using a silica gel having a stationary phase of 200 mesh. The eluent was dichloromethane/methanol, wherein the volume ratio of dichloromethane to methanol was gradually increased from 50:1 to 15:1, and the eluate was concentrated and dried to obtain 18.9 mmol of hydroxychloroquinolinone 11.3 g, the yield was 52.5%.

[0036] Example 2

[0037] 8.7 g of hydroxychloroquine 20 mmol was weighed and placed in a 250 mL one-neck round bottom flask, and 60 mL of water was added thereto, followed by stirring at room temperature. A 20 mL portion of a 20% aqueous sodium hydroxide solution was slowly added dropwise, and a large amount of a white oil was obtained. A white oil was dissolved in ethyl acetate (40 mL), and the organic phase was separated. The aqueous phase was extracted twice with ethyl acetate. The organic phase was washed with 50 mL of saturated sodium chloride aqueous layer and dried over anhydrous sodium sulfate.

[0038] Under nitrogen protection and ice bath cooling, 19.2 mmol of a-linolenic acid 7.6 g and 100 mL of dichloromethane with a purity of 70% were added to a 250 mL three-neck round bottom flask, and an appropriate amount of 4-dimethylaminopyridine and bicyclo was sequentially added. The hexylcarbodiimide was stirred for 60 minutes, and the reaction system was heated to normal temperature. An appropriate amount of triethanolamine and hydroxychloroquine 6.5 g of 19.2 mmol was added, and the reaction was stirred for 24 hours. 50 mL of methylene chloride was added to the flask, and the reaction solution was filtered. The filtrate was placed in an ice box, and after standing for a while, the reaction solution was filtered, and the process was carried out 5 times. The dried filtrate was concentrated to give a brown oil. The oil was dissolved in 80 mL of ethyl acetate and transferred to a separatory funnel. The solution was washed with a solution of hydrochloric acid (80 mL). The mixture was separated into three phases, the upper layer was methyl t-butyl ether phase, the middle

layer was oily, and the lower layer was The aqueous phase was separated, and the oil was separated and dissolved in 100 mL of methanol. Decolorization was carried out by adding activated carbon. After decolorization, column chromatography was carried out using a silica gel having a stationary phase of 300 mesh. The eluent was dichloromethane/methanol, and the volume ratio of dichloromethane to methanol was determined. Increasingly from 50:1 to 15:1, after elution, it was concentrated to give hydroxychloroquinolinate 5.8 g of 9.7 mmol in a yield of 50.5%.

CN110283121
Hydroxychloroquine synthetic method
[PDF]

Abstract
The invention provides a hydroxychloroquine synthetic method, including the steps of mixing 4,7-dichloroquinoline, 2-[(4-aminopentyl)(ethyl)amino]ethanol and N,N-diisopropylethylamine, reacting under protective gas, and after the reaction, performing extraction, concentration and purification to obtain the hydroxychloroquine. By using the synthetic method provided by the invention, N,N-diisopropylethylamine is used as both an acid-binding and a solvent to promote smooth reaction, the amount is small (only theoretical amount), and the consumption is low; the reaction time is short, alkalization is not needed after treatment, the hydroxychloroquine can be obtained by just the operations of extraction and recrystallization, and the operation is simple; the extraction solvent and the recrystallization solvent may be the same solvent, which is beneficial to the recovery and utilization of the solvent, and the production cost is reduced; the total recovery is increased from 45.9% to 74.7%, the product quality is increased from 99.0% to 99.8% or above (HPLC purity), and single impurity being less than or equal to 0.1%.

[0001] Technical field

[0002] The present invention relates to the field of medicinal chemistry, and in particular to the preparation of hydroxychloroquine for use in the treatment of malaria, rheumatoid arthritis and systemic lupus erythematosus.

[0003] Background technique

[0004] Hydroxychloroquine (1) is a 4-aminoquinolone compound, chemical name 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol, chemical structure as follows:

[0005]

[0006] 1951In the year, hydroxychloroquine was successfully developed by Winthrop. It was originally used for malaria treatment. It was used to treat systemic lupus erythematosus in 1955. It was first introduced in the United States in 1956, and then successively in Japan, France, Denmark, Finland, Germany, etc. National and regional listings. In 1998, the US FDA approved hydroxychloroquine for the treatment of rheumatoid arthritis and lupus erythematosus. Compared with other similar drugs, it has an advantage in safety, not only can improve the symptoms of arthritis in patients, but also anti-oxidation and anti-lipid, avoid platelet aggregation, reduce the blood sugar level of patients, and accelerate the rate of insulin secretion. In addition, to improve the overall sensitivity of insulin, in the treatment of

dermatomyositis, lichen planus, AIDS, etc. also have a positive effect.

[0007] US 2,546,658 discloses a process for the synthesis of hydroxychloroquine, the process of which is as follows:

[0008] Using 4,7-dichloroquinoline (2) and 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine (3) as raw materials, using phenol as solvent and sodium iodide as catalyst After stirring at 125-130 ° C for 18 h, the reaction solution was cooled, methanol was added, then filtered with charcoal, the filtrate was added with phosphoric acid, the wall was rubbed with a glass rod, allowed to stand for 2 days, suction filtered, and the filter cake was rinsed with methanol. After drying, hydroxychloroquine diphosphate was obtained in a yield of 41.9% (in terms of 2). The obtained hydroxychloroquine phosphate was dissolved in water, dissociated with ammonium hydroxide, extracted with chloroform, and the chloroform was evaporated under reduced pressure. The residue was crystallised from diethyl ether to afford hydroxy chloroquine (1), yield: 44. Diphosphate meter). The specific route is as follows:

[0009]

[0010] The method mainly has the following disadvantages: i) the reaction uses phenol as a solvent, the phenol is highly toxic and corrosive, and is extremely harmful to people and the environment, and is converted into an aqueous solution of sodium phenolate to form harmful phenol-containing wastewater in the post-treatment process. Increased the difficulty of the three waste treatment; ii) the condensation reaction time is 18h, the long-term reaction will not only increase the production cost, but also lead to the increase of the content and quantity of impurities, especially the long-term high temperature reaction, which will increase the deethylated impurities. Produced, and this impurity is difficult to remove; iii) use of phosphoric acid to remove impurities during the reaction, resulting in the production of a large amount of phosphorus-containing wastewater, further increasing environmental pressure; iv) extraction solvent chloroform is a type of solvent, carcinogenic, environmentally unfriendly; v) Recrystallization solvent Ether is flammable and explosive, and has a high safety hazard; vi) The procedure is long, the operation is cumbersome, and the total yield is very low, only 18.6%.

[0011] CA2561987A1 discloses a method for synthesizing hydroxychloroquine sulfate, and the reaction process of the method is as follows:

[0012]

[0013] The method has the advantages of long steps, complicated operation and high cost; the condensation reaction time is as long as 20-24 hours, which leads to an increase in the content and quantity of impurities, resulting in lower product quality.

[0014] WO2005062723A2 discloses a method for synthesizing hydroxychloroquine sulfate, the reaction process of which is as follows:

[0015]

[0016] The reaction time is too long (45-50h), and the energy consumption is large, which not only increases the production cost, but also increases the generation of impurities, which is not conducive to industrial production; in the post-treatment process, the product is firstly

made into phosphate and then alkalized with ammonium hydroxide. The product is freed, extracted with dichloromethane, the operation is cumbersome, and a large amount of phosphorus-containing wastewater is generated, which increases the pressure of “waste water” treatment; in particular, the final product is obtained by column chromatography, the operation is complicated, the cost is high, and it is not suitable for industrial large-scale production. .

[0017] US 5,314,894 discloses a method for synthesizing hydroxychloroquine sulfate, the reaction process of which is as follows:

[0018]

[0019] A large amount of high-boiling N-ethyldiisopropylamine is used as a reaction solvent in the method, which is difficult to recover, easily leads to solvent residue affecting product purification, and increases environmental protection cost; condensation reaction time is too long (48h), energy consumption is very large And increase the production of impurities; post-treatment requires alkalization, re-extraction, drying, concentration, column, fractionation, etc. to obtain the product, many steps, complicated operation, low yield (only 45.9%); the final product passed Column chromatography and fractional distillation are two steps, the operation is cumbersome, the cost is high, and it is not suitable for industrial large-scale production.

[0020] CN107266323A discloses a method for synthesizing hydroxychloroquine sulfate, and the reaction process of the method is as follows:

[0021]

[0022] The method uses carcinogenic chloroform as a solvent, and the amount is large, which is extremely harmful to people and the environment; the use of high-boiling N,N-dimethylformamide as a solvent is difficult to recycle, and the wastewater is greatly affected. The environmental protection pressure; the route is long and complicated, the operation is cumbersome; the raw materials are expensive and the cost is high.

[0023] Each of the above routes has shortcomings such as long reaction time, large reagent toxicity, cumbersome operation, environmental pollution, high production cost, and poor product quality. It is difficult to achieve safe and environmentally friendly green production requirements, lack market competitiveness, and is not suitable for industrial production. Especially with the increase of production capacity, the environmental protection cost has risen sharply. Therefore, it is urgent to study a green synthetic route suitable for industrial production, with the aim of solving the problems of low greening, low yield and low product purity in the current process.

[0024] Summary of the invention

[0025] The object of the present invention is to overcome the deficiencies in the prior art and to provide a method for synthesizing hydroxychloroquine suitable for green synthesis in industrial production.

[0026] In order to achieve the above object, the present invention provides a method for synthesizing hydroxychloroquine, which comprises the steps of:

[0027] Mixing 4,7-dichloroquinoline, 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine with N,N-diisopropylethylamine, and reacting under protective gas After the reaction is completed, extraction, concentration, and purification are carried out to obtain hydroxychloroquine.

[0028] Preferably, the method of synthesis comprises an extraction step to extract hydroxychloroquine.

[0029] Preferably, the extraction solvent used in the extraction step is a single solvent or a mixed solvent of isopropyl acetate, ethyl acetate, dichloromethane, methyl tert-butyl ether, toluene or methyl isobutyl ketone. Isopropyl acetate is preferred.

[0030] Preferably, in the synthesis method, after the reaction is completed, alkalization is not required, direct extraction, concentration, and cooling and crystallization are carried out to obtain crude hydroxychloroquine.

[0031] Preferably, the method of synthesis comprises a recrystallization step of crude hydroxychloroquine to refine hydroxychloroquine.

[0032] Preferably, the recrystallization solvent used in the recrystallization step is a single solvent or a mixed solvent of isopropyl acetate, ethyl acetate, acetone, methyl tert-butyl ether, toluene or methyl isobutyl ketone. Isopropyl acetate is preferred.

[0033] Preferably, the shielding gas is nitrogen, argon, or helium.

[0034] Preferably, the reaction time is 4 to 15 h, preferably 8 to 10 h; the reaction temperature is 90 to 160 ° C, preferably 125 to 135 ° C, and the reaction temperature is preferably gradually increased.

[0035] Preferably, the molar ratio of 4,7-dichloroquinoline to 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine is 1:2.5 to 1:0.8, preferably 1:1.2. ~1:1.6.

[0036] Preferably, the molar ratio of 4,7-dichloroquinoline to N,N-diisopropylethylamine is from 1:1.5 to 1:0.8, preferably 1:1.

[0037] The advantages of the method for synthesizing hydroxychloroquine and its sulfate provided by the present invention are as follows:

[0038] 1)Avoid the use of corrosive and carcinogenic phenol as a reaction solvent, and avoid the use of carcinogenic dichloroethane and chloroform as extraction solvents or recrystallization solvents.

[0039] 2)The extracting agent and the recrystallization solvent can use the same solvent such as isopropyl acetate, which is advantageous for recycling and reducing the production cost.

[0040] 3)The use of shielding gas effectively controls the generation of various types of oxidizing impurities; the short reaction time greatly reduces the generation of impurities such as deethylated impurities.

[0041] 4)The total yield increased from 45.9% to 74.7%, and the product quality increased

from 99.0% to 99.8% (HPLC purity), and the single impurity was ≤0.1%, which greatly improved the market competitiveness of the product.

[0042] 5)The theoretical amount of N,N-diisopropylethylamine is used as an acid anhydride and as a reaction solvent to promote the smooth progress of the reaction, while the amount is small, the loss is low, and the cost is lowered;

[0043] 6)The post-treatment does not require alkalization, and high-quality hydroxychloroquine can be obtained in a high yield only by operations such as extraction and recrystallization, thereby avoiding complicated operations such as column and fractionation, greatly simplifying the process and reducing the cost;

[0044] 7)The reaction conditions are mild, the operation is simple, the equipment requirements are low, and it is suitable for industrial production.

[0045] 8)The process has completed four batches of pilot-scale amplification experiments, and the pilot test is stable.

[0046] detailed description

[0047] For a better understanding of the contents of the present invention, further description will be made below in conjunction with the specific embodiments. This embodiment is implemented on the premise of the technical solution of the present invention, and detailed implementation manners and specific operation procedures are given, but the scope of protection of the present invention is not limited to the following embodiments.

[0048] The present invention provides a specific hydroxychloroquine reaction route as follows:

[0049]

[0050] Melting point, mass spectrum and NMR result of hydroxychloroquine: melting point: 90.9-91.9 ° C; ESI-MS (m/z): 336.2 [M+H]+; 1H NMR (400 MHz, CDCl3) δ ppm: 8.51 (d, J=5.5 Hz, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 9.0, 2.2 Hz, 1H), 6.4 (d, J = 5.5 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 3.72 (p, J = 6.5 Hz, 1H), 3.6 (t, J = 5.1 Hz, 2H), 2.63 (m, 4H), 2.6 (m,1H), 2.56 (t, J = 6.4 Hz, 2H), 1.80 - 1.59 (m, 4H), 1.33 (d, J = 6.4 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H)

[0051] Example:

[0052] 4,7-dichloroquinoline (500 g, 2.5 mol), 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine (5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine) was added to a 3000 mL three-necked flask equipped with a reflux condenser. 668g, 3.8mol) and N,N-diisopropylethylamine (323g, 2.5mol), pass nitrogen protection, start mechanical stirring, slowly warm to 125 ~ 135 ° C reflux reaction for 8h; cool the reaction solution, to be concentrated The liquid was cooled to below 50 ° C, and 1500 mL of water was added; after stirring for 15 minutes, the reaction liquid was cooled to below 40 ° C, extracted with isopropyl acetate (3000 mL * 3), and the organic phase was washed with water (3000 mL * 2), and washed with saturated brine (3000mL*1), 2/3 isopropyl acetate was recovered under reduced pressure, then slowly reduced to 0～5°C for 1h; filtered with Buchner funnel to

obtain 801g (wet weight) of off-white solid, and then isopropyl acetate Crystallization gave a wet weight of 710 g of a white powdery solid, which was dried under vacuum at 40 ° C for 6 h to afford 627 g (HPLC: 99.83%) as a white solid.

CN109456266
Novel preparation method of hydroxychloroquine sulfate
[PDF]

Abstract
The invention discloses a preparation method of hydroxychloroquine sulfate. The preparation method is characterized in that a parent core 4,7-dichloroquinoline used as a starting material and a hydroxychloroquine side chain 5-(N-ethyl-N-2- ethanolamine)-2-amylamine undergo condensation reaction in the presence of a catalyst to obtain a hydroxychloroquine free base, and then the hydroxychloroquinefree base undergoes salt formation with sulfuric acid to obtain the hydroxychloroquine sulfate. The preparation method overcomes the disadvantages in the prior art, and has the advantages that the useamount of the side chain is reduced; the total yield is more than or equal to 90 percent; the yield of the hydroxychloroquine sulfate is more than or equal to 96 percent; the total yield is more thanor equal to 86 percent; the purity of the hydroxychloroquine sulfate is more than 99. 7 percent; and the single impurity is less than 0.1 percent. The preparation method meets the pharmacopoeia requirements and is short in reaction time, easy and convenient to operate, low in pollution, low in cost and suitable for industrial production.

[0001] Technical field

[0002] The invention belongs to the field of medicine and chemical technology, and specifically designs a medicine for treating discoid lupus erythematosus and systemic lupus erythematosus - hydroxychloroquine sulfate.

[0003] Background technique

[0004] Hydroxychloroquine Sulfate (HCQ) is chemically known as 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-ethanol sulfate, CAS No. 747-36- 4. The chemical structure is as follows:

[0005]

[0006] Hydroxychloroquine sulfate was successfully developed by Winthrop and first listed in the United States in 1956. It was later listed in France, Denmark, Japan, Germany, Finland and other countries and regions. On May 29, 1998, the US FDA approved hydroxychloroquine sulfate tablets for the treatment of lupus erythematosus and rheumatoid arthritis.

[0007] US 2,546,658 discloses a process for the synthesis of hydroxychloroquine sulfate, the process of which is as follows:

[0008]

[0009] The patent was published in 1951, the process is relatively backward, the use of

phenol as a solvent, phenol pollution is large, phenol-containing wastewater is a kind of pollution in industrial wastewater, and phenol is solid at room temperature, must be heated into liquid to produce, The operation is cumbersome, the recovery is difficult, the post-processing difficulty is increased, the yield is low, less than 20%, and the product is difficult to handle, and is not suitable for industrial production.

[0010] CA2561987 discloses a process for preparing hydroxychloroquine sulfate, the reaction process of which is as follows:

[0011]

[0012] The method comprises the steps of sequentially adding isopropanol, hydroxychloroquine side chain, 4,7-dichloroquinoline, stirring, slowly heating, slowly distilling off isopropanol, stirring at 120-130 ° C for 20-24 h, then cooling to 70-80 Add water and methyl isobutyl ketone, adjust the pH to above 10, separate the liquid, add acetic anhydride at room temperature and stir overnight, then add lithium hydroxide monohydrate, water and methanol, stir again at room temperature overnight, and wash the organic phase again with water. Once, methanol and sulfuric acid are added to the organic phase, and the mixture is filtered with salt to obtain crude hydroxychloroquine sulfate. The crude product is added to water and methyl isobutyl ketone, stirred and dissolved, and the pH is adjusted to 10-11 by adding sodium hydroxide. The liquid phase is separated, and the organic phase is washed with brine, decolorized by adding activated carbon, filtered, and the filtrate is evaporated to obtain hydroxychloroquine free base, and salt is formed with concentrated sulfuric acid in an anhydrous alcohol to obtain a hydroxychloroquine sulfate product. The purification process of the method is cumbersome, the route is long, the waste water and the waste solid amount are large, and it takes two steps to form salt, which takes a long time and is not suitable for process production.

[0013] WO2010027150 discloses a method for synthesizing hydroxychloroquine sulfate, the reaction route of which is as follows:

[0014]

[0015] The method comprises adding 4,7-dichloroquinoline, a hydroxychloroquine side chain to an autoclave, pressurizing with nitrogen or argon to 5-20 bar, and reacting at 100-120 ° C for 4-6 hours. After the reaction was completed, hydrochloric acid was added to adjust the acidity, and impurities were extracted by chloroform extraction. The aqueous phase was adjusted with alkali and then extracted with chloroform. The chloroform was evaporated, crystallised from dichloroethane, and concentrated sulfuric acid was added under anhydrous ethanol to obtain hydroxychloroquine sulfate. The reaction involves high pressure, and there are certain safety hazards. The alkalization loss is large after acidification first, and chloroform is a second type solvent. Dichloroethane is a kind of solvent and should be controlled.

[0016] CN103724261A discloses an industrial process for the production of hydroxychloroquine sulfate:

[0017]

[0018] The method comprises: under nitrogen protection, 4,7-dichloroquinoline is directly

condensed with a hydroxychloroquine side chain at a high temperature for 13-24 hours, then acidification and impurity removal, alkalization extraction, crystallization to obtain hydroxychloroquine free base, and then Hydrolysis with concentrated sulfuric acid in an alcohol solution gives hydroxychloroquine sulfate. The method is directly mixed and heated by a solvent-free method, and impurities of side chain dehydration polymerization are easily generated during the reaction, and 4,7-dichloroquinoline is easily sublimed at a high temperature, and heating for a long time causes 4,7-dichloroquinoline from the reaction system. Sublimation in the middle, affecting the yield, after the end of the reaction, it is necessary to first adjust the acid, then alkalized, the operation is cumbersome, the waste water and waste solid amount are large, and the operation is cumbersome, and is not suitable for industrial production.

[0019] CN102050781 discloses a process for preparing hydroxychloroquine sulfate. Similar to CA2561987, it is necessary to slowly distill off the reaction solvent, and it is necessary to control the distillation temperature and time, the reaction requires a large amount of solvent, and the temperature control process and the solvent are precisely controlled in industrial production. The steaming process is more difficult.

[0020] CN104230803 discloses an industrial preparation method of hydroxychloroquine sulfate. The condensation reaction of 4,7-dichloroquinoline with hydroxychloroquine side chain is carried out by distilling off the solvent under the catalysis of sodium alkoxide. Under high temperature conditions, sodium alkoxide will undergo nucleophilic substitution with 4,7-dichloroquinoline to form an ether product, which is difficult to remove, affecting the purification of hydroxychloroquine free base, and the alcoholic hydroxyl group on the side chain is in sodium alkoxide. In the presence of hydroxy anion, 4,7-dichloroquinoline produces by-products, which makes purification difficult, and the reaction should control the temperature rising process and solvent evaporation rate, and the operation is difficult.

[0021] In the preparation method of the above-disclosed hydroxychloroquine sulfate, there are disadvantages, so it is necessary to find an industrial preparation method which is simple in operation, high in efficiency, high in yield and high in quality, and environmentally friendly.

[0022] BRIEF DESCRIPTION OF THE DRAWINGS Figure 1 is a high performance liquid chromatogram of hydroxychloroquine sulfate.

[0023] Summary of the invention

[0024] The invention relates to a novel preparation method of hydroxychloroquine sulfate, which is prepared by dissolving 4,7-dichloroquinoline and hydroxychloroquine side chain under the protection of an inert gas in a substituted benzene or other strong polar solvent and heating and condensing under heating. After crystallization, hydroxychloroquine free base is obtained, and then salt is formed with sulfuric acid to obtain hydroxychloroquine sulfate. The reaction route is as follows:

[0025]

[0026] 1.The shielding gas may be nitrogen, argon or helium, preferably nitrogen.

[0027] 2.The mass ratio of 4,7-dichloroquinoline to the side chain is 1:1-1.2.

[0028] 3.The catalyst is a self-made alumina-supported fluoride salt: wherein the fluorine salt may be an organic fluoride salt or an inorganic fluoride salt, and is selected from the group consisting of sodium fluoride, potassium fluoride, cesium fluoride, etc., and potassium fluoride is preferred.

[0029] 4.The reaction solvent may be a substituted benzene such as toluene, chlorobenzene or xylene, or an aprotic strong polar solvent such as dimethyl sulfoxide or N,N-dimethylformamide. The solvent is used in an amount of from 3 times to 5 times the amount of 4,7-dichloroquinoline. The reaction temperature is 100-150 degrees and the reaction time is 4-12 hours.

[0030] 5.The hydroxychloroquine free base can be purified by crystallization using an acetate, and may be selected from ethyl acetate, isopropyl acetate, n-butyl acetate, and preferably ethyl acetate.

[0031] 6.Hydroxychloroquine free base is salted with sulfuric acid in an aqueous alcohol solution to obtain hydroxychloroquine sulfate. The alcohol may be selected from the group consisting of methanol, ethanol, and propanol. The alcohol concentration may be 60% to 75%, and the salt formation temperature may be 0-20. Degree, the reaction time can be 8~12h.

[0032] The advantages of the invention are as follows:

[0033] 1. The amount and type of organic solvent used in the reaction are reduced, the cost is reduced, and environmental friendliness is improved.

[0034] 2. Avoid the use of toxic catalysts, atmospheric reactions, and shorten the reaction time

[0035] 3. High yield, simple post-treatment, simple operation steps, suitable for industrial production

[0036] 4. The salt formation process uses controlled crystallization to avoid inclusion of impurities.

[0037] 5. The hydroxychloroquine yield obtained by the invention is ≥90%, the liquid phase purity is ≥99.7%, the hydroxychloroquine sulfate yield is ≥96%, the total yield is ≥86%, the hydroxychloroquine sulfate purity is greater than 99.7%, the single impurity is less than 0.1%, the melting point It is 239 ° C ~ 240 ° C. Both yield and purity are high, which in turn reduces production costs and pollution control costs.

[0038] The industrial preparation method of hydroxychloroquine sulfate of the present invention is further illustrated and explained below by way of examples without limiting the scope of the invention.

[0039] Example 1: Preparation of Alumina Supported Potassium Fluoride

[0040] 10 g of anhydrous potassium fluoride, 30 g of 200-mesh alumina powder was dissolved in 100 ml of water, ultrasonically stirred at 50 Hz for 45 min, and dried under reduced pressure at 55 ° C to obtain a solid powder, which was vacuum dried at 120 ° C for 8

hours, and then ground to a powder. Thereafter, 40 g of a catalyst was obtained.

[0041] Example 2: Preparation of Alumina Supported Tetrabutylammonium Fluoride

[0042] 40 g of tetrabutylammonium fluoride, 40 g of 200-mesh alumina powder was dissolved in 100 ml of water, ultrasonically stirred at 50 Hz for 45 min, and the water was evaporated to dryness under reduced pressure at 55 ° C to obtain a solid powder, which was vacuum dried at 130 ° C for 8 hours, and then ground into Powder, 80 g of catalyst was obtained.

[0043] Example 3: Preparation of alumina supported cesium fluoride

[0044] 10 g of cesium fluoride, 20 g of 200-mesh alumina powder, dissolved in 100 ml of water, ultrasonically stirred at 50 Hz for 1 hour, and dried under reduced pressure at 55 degrees to obtain a solid powder, dried under vacuum at 100 degrees for 4 hours, and then ground to a powder. , 30 g of catalyst was obtained.

[0045] Example 4: Preparation of hydroxychloroquine free base

[0046] 1 kg of 4,7-dichloroquinoline, 1 kg of hydroxychloroquine side chain, 1.8 kg of potassium fluoride supported by alumina, dissolved in 5 kg of toluene, heated to 110-120 ° C, reacted for 12 h, completely detected by TLC, cooled, evaporated to dryness Toluene, 5 kg of ethyl acetate was added, and the mixture was heated to reflux. The mixture was filtered while stirring, and the filtrate was stirred and cooled for 3 hr. and filtered, and the filter cake was washed twice with ethyl acetate and dried to give 1.6 g of hydroxychloroquine free base, yield 94%. The purity is 99.7%, and the melting point is 89-90 °C.

[0047] Example 5: Preparation of hydroxychloroquine free base

[0048] 1 kg of 4,7-dichloroquinoline was dissolved in 3 kg of dimethyl sulfoxide, 3.5 kg of alumina-supported cesium fluoride was added, heated to 125 degrees, stirred for 4 hours, cooled to 50-60 ° C, and hydroxychloroquine was added. 1.2kg side chain, raised to 125 ° C, heated for 8 hours, cooled to room temperature, suction filtration, 15kg water was added to the filtrate, extracted with 3kg of dichloromethane three times, evaporated to dryness, added with 3kg of isopropyl acetate and stirred to obtain hydroxychloroquine free The base is 1.55 kg, the yield is 91.39%, the purity is 99.5%, and the melting point is 87-89 °C.

[0049] Example 6: Preparation of hydroxychloroquine free base

[0050] 1 kg of 4,7-dichloroquinoline, 1 kg of hydroxychloroquine side chain, dissolved in 5 kg of chlorobenzene, 3.96 kg of alumina-supported tetrabutylammonium fluoride, heated under reflux for 12 hours, completely detected by TLC, cooled, steamed Dry chlorobenzene, adding 5 kg of ethyl acetate, heating under reflux, hot suction filtration, the filtrate was stirred and cooled to 30 °C, stirring was continued for 3 hours, suction filtration, the filter cake was washed twice with ethyl acetate, and dried to give hydroxychloroquine free base 1.59 kg, yield 93.75%, purity 99.6%, melting point 87-90 ° C.

[0051] Example 7: Preparation of hydroxychloroquine sulfate

[0052] 1 kg of hydroxychloroquine free base was dissolved in 5 L of 70% ethanol, cooled to

0-5 ° C, and 0.32 kg of concentrated sulfuric acid was added dropwise. After the completion of the dropwise addition, stirring was continued for 1 hour, and the mixture was stirred at room temperature for 12 hours. The crystals were slowly precipitated and suction filtered. The filter cake was washed once with 70% ice ethanol and dried to give 1.24 kg of white crystals.

[0053] Example 8: Preparation of hydroxychloroquine sulfate

[0054] 1 kg of hydroxychloroquine free base was dissolved in 5 L of 75% methanol, cooled to 0-5 degrees, and 0.32 kg of concentrated sulfuric acid was added dropwise. After the completion of the dropwise addition, stirring was continued for 1 hour, and the mixture was stirred at room temperature for 10 hours. The crystals were slowly precipitated and suction filtered. The filter cake was washed once with 75% ice methanol and dried to give 1.25 kg of white crystals.

[0055] Example 9: Preparation of hydroxychloroquine sulfate

[0056] 1 kg of hydroxychloroquine was dissolved in 5 L of 60% isopropanol, cooled to 0-5 degrees, and 0.32 kg of concentrated sulfuric acid was added dropwise. After the completion of the dropwise addition, stirring was continued for 1 hour, and the mixture was stirred at room temperature for 12 hours. The crystals were slowly precipitated and suction filtered. The filter cake was washed once with 60% ice isopropanol and dried to give 1.23 kg of white crystals.

WO2010027150
NEW PREPARATION OF HYDROXYCHLOROQUINE
[PDF]

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

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).

[Reaction Scheme 1]

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%.

Further, CA Patent No. 2,561,987 teaches a process for preparing hydroxychloroquine, 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.

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

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.

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.

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.

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:

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.

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.

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.

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

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

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.

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

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

; and

(b) reacting the hydroxychloroquine of Step (a) with sulfuric acid (H 2 SO 4) to obtain hydroxychloroquine sulfate.

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

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

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.

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.

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.

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).

Example 1: Preparation of hydroxychloroquine using pressure of 20 bars

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.

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)

Example 2: Preparation of hydroxychloroquine (formula 1) using pressure of 10 bars

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.

1 H NMR (500 MHz) values of the obtained compound were identical with those as in Example 1.

Example 3: Preparation of hydroxychloroquine sulfate

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.

1 H NMR (300 MHz): δ(D 2 O) 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)

Example 4: Preparation of hydroxychloroquine sulfate

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.

1 H NMR (500 MHz) values of the obtained compound were identical with those as in Example 3.

Hydroxychloroquine Therapy Patents

CN103096891A
Treatment of hepatitis c virus related diseases using hydroxychloroquine or a combination of hydroxychloroquine and an anti-viral agent

Therapeutically effective amounts of hydroxychloroquine are disclosed which are sufficient to inhibit HCV-induced autophagy in the subject. An anitviral agent may be co-administered with the hydroxychloroquine. Methods utilizing synergistic combinations of hydroxychloroquine and an antiviral agent are disclosed. Further disclosed are compositions comprising hydroxychloroquine and an antiviral agent, as well as hydroxychloroquine and uses ...

The invention belongs to the technical field of biomedicine, and relates to new application of chloroquine or a derivative hydroxychloroquine medicine, in particular to application of chloroquine or derivative hydroxychloroquine in medicine for treating Graves eye diseases. The invention proves... acid synthesis of fibroblasts; the effects are superposed to show that: the chloroquine and the derivative hydroxychloroquine thereof can effectively ...

US2020046860
Systems and Methods for the Detection of Hydroxychloroquine-Mediated Cardiotoxicity

A method for detecting hydroxychloroquine-mediated cardiotoxicity in a subject. The method can comprise administering a radiotracer to the subject and acquiring an image to detect the presence or absence of hydroxychloroquine-mediated cardiotoxicity in the subject.

US2002091139A1 / WO9817231A2
Treatment and delivery of hydroxychloroquine

The treatment of various disease states with hydroxychloroquine ...

CN110638818A
Application of chloroquine or derivative hydroxychloroquine

CN107456455A
Medicinal composition capable of preventing or treating inflammatory diseases

CN110638818A
Application of chloroquine or derivative hydroxychloroquine
CN109125609
Traditional Chinese medicinal composition for treating malaria of pet dogs and preparation method

CN109288816
Chloroquine gel and preparation method and application thereof

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4,7-DiChloroQuinoline Synthesis

CN109928925
Sublimation purification method of 4,7-dichloroquinoline
[PDF]

Abstract
The invention discloses a sublimation purification method of 4,7-dichloroquinoline. The method is characterized in that a sublimation method is adopted for purifying the 4,7-dichloroquinoline to prepare high-purity 4,7-dichloroquinoline. According to the method disclosed by the invention, the defect of a 4, 7-dichloroquinoline purification method adopting solvent crystallization can be overcome, an organic solvent is not introduced, pollution is avoided, the purity of the purified 4, 7-dichloroquinoline is high, the appearance is good; the purification method is simple and convenient to operate and suitable for industrial production.

CN110627716
Preparation method of 4,7-dichloroquinoline
[PDF]

Abstract
The invention discloses a preparation method of 4,7-dichloroquinoline, and belongs to the technical field of synthesis of antimalarial drug intermediates. According to the method, 7-chloro-4-hydroxyquinoline is used as a raw material and reacts with triphosgene under the action of a catalyst to generate the 4,7-dichloroquinoline. The synthetic method provided by the invention can effectively avoidthe use of chlorinating agents unfriendly to the environment, such as phosphorus oxychloride and thionyl chloride, reduces the pollution to the environment and the corrosion to equipment, and reducesthe production costs.

CN103626699
Industrial preparation method of 4,7-dichloroquinoline
[PDF]

Abstract
The invention relates to a preparation method of a medical intermediate 4,7-dichloroquinoline. The 4,7-dichloroquinoline is an important intermediate of a medicine hydroxychloroquine sulfate for treating discoid lupus erythematosus and systemic lupus erythematosus. The preparation method comprises the following steps: performing hydrolysis and acid adjustment on 4-hydroxyl-7-chlorine-quinoline-3-carboxylic acid ethyl ester by using 10% sodium hydroxide solution to prepare 4-hydroxyl-7-chlorine-quinoline-3-carboxylic acid; performing decarboxylation to produce 4-hydroxyl-7-chloroquinoline; and chlorinating the 4-hydroxyl-7-chloroquinoline by using phosphorus oxychloride to obtain 4,7-dichloroquinoline crude products; and performing one-step refining to obtain the products. The purity of the prepared products is more than or equal to 99% and the total yield

of the products is more than or equal to 70%; raw materials are easily available; the process is simple; the yield and the purity are high in each step; and the preparation method is suitable for industrialized production.

IN155649B A PROCESS FOR THE PREPARATION OF 4,7-DICHLOROQUINOLINE
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IN155650B A PROCESS FOR THE PREPARATION OF 4,7-DICHLOROQUINOLINE
