RESEARCH ARTICLE OPEN ACCESS

Study of Manufacturing of Hydroxychloroquine

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ABSTRACT
Hydroxychloroquine belongs to the antimalarial medication class. It kills the parasitic germs that cause malaria. Hydroxychloroquine may help treat rheumatoid arthritis and systemic lupus erythematosus by lowering immune system activity. Hydroxychloroquine does not work against all types of malaria or in places where the illness has become resistant to a similar medicine called chloroquine. The reaction of 4,7-dichloroquinoline with 2-amino(5- diethylamino) pentene produces hydroxychloroquine.

Keywords **–** Hydroxychloroquine, COVID-19, Anti-malarial Drug, DMARDs, Chronic Threat

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I. INTRODUCTION

1.1 WHAT IS HYDROXYCHLOROQUINE?

Hydroxychloroquine (HCQ) is an antimalarial medicine used to prevent malaria from being transmitted by mosquito bites. The medicine is also used to treat lupus erythematosus, Q fever, rheumatoid arthritis, the recently identified COVID 19 illness, and malaria. In conjunction with the common antibiotic azithromycin, the antibiotic hydroxychloroquine may be used to treat COVID 19. It is available over the counter in places such as India and is reasonably priced. However, as it is being evaluated for the treatment of the recently found condition COVID-19, its purchase is carefully limited

1.2 GLOBAL SCENARIO OF HYDROXYCHLOROQUINE?

The worldwide hydroxychloroquine market is booming, as the medicine is being investigated as a possible therapy for the COVID-19 pandemic. Furthermore, the increased frequency of autoimmune illnesses such as rheumatoid arthritis and lupus erythematosus throughout the world is propelling market expansion. In recent years, rising malaria rates in developing and poor nations, such as India and Africa, have raised medication manufacturing even more. According to WHO research, 19 African nations and India accounted for over 85% of the worldwide malaria burden. However, the market's expansion may be hampered by hydroxychloroquine's possible negative effects over the projection period. During the projected period, the worldwide hydroxychloroquine market is expected to grow at a CAGR of 4%. (2020-2030). The current COVID-19 pandemic has boosted demand for hydroxychloroquine medications, which can be utilized as a therapeutic option. The worldwide hydroxychloroquine market is booming, as medicine is being examined as a possible therapy for the global pandemic illness COVID-19. According to C (IPA) secretary-general Sudarshan Jain, India manufactures 70% of the world's supply of hydroxychloroquine. The country has monthly hydroxychloroquine (HCQ) manufacturing capacity of 40 tons, which translates to 20 crore 200-mg tablets. Furthermore, because the medicine is also used to treat auto-immune illnesses such as rheumatoid arthritis and lupus, producers have adequate manufacturing capacity that may be expanded. Hydroxychloroquine is extremely similar to chloroquine, one of the most well-known anti malarial medications, although it has fewer adverse effects. It is readily available and reasonably priced over the counter. The country that exports the most medicine is India. Officials said India would only export the medication if all local conditions were met.

II. LITERATURE SURVEY

1.1 Hydroxychloroquine synthetic method CN110283121 (A)

➢INVESTORS
1. ZHAO JIANHO NG;
2. CHEN CHUNY AN;
3. YU KUNJIA O;
4. QIU WENME I;
5. YAN GUOMI NG;
6. YU WEI;
7. LIJIE;
8. LIU FANGY ON G;

9. LIU ZIYUE;

The invention provides a hydroxychloroquine synthetic method, including the steps of mixing 4,7- dichloroquinoline, 2[(4aminopentyl) (ethyl)amino] ethanol, and N, N diisopropylethylamine, reacting under protective gas, and after the reaction, performing extraction, concentration and purification to obtain 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 a smooth reaction, the amount is small (only a 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%.

1.2 NEW PREPARATION OF HYDROXYCHLOROQUINE /KR20100 0293 32(A)

➢INVESTORS

I. MIN YUN SIK;
II. CHO HYUN SUNG;
III. MOKIL WOONG

A method for preparing hydroxychloroquine is provided to suppress the generation of by-products by reducing reaction temperature and time and preparing the hydroxychloroquine with high yield and purity.

➢CONSTITUTION

Hydroxychloroquine of chemical formula 1 is prepared by reacting N'ethyl-N'β hydroxyethyl-1,4-pentadiamine combined with 4,7 dichloroquinoline at high pressure. The high pressure is over 5bar.

10. XU XIAOLI

The reaction condition is 100-120°C for six hours. A method for preparing hydroxychloroquine sulfate

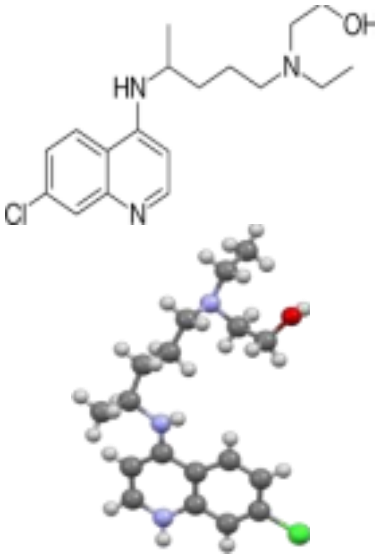
➢COMPRISES:

A step of reacting N'ethyl-N' β- hydroxyethyl 1,4-pentadiamine with 4,7 dichloroquinoline to obtain hydroxychloroquine and a step of reacting sulfuric acid with hydroxychloroquine to obtain hydroxychloroquine sulfate.

III. FIGURES AND TABLES

3.1 HOW HYDROXYCHLOROQUINE WORKS

Hydroxychloroquine is in a class of drugs called antimalarials. It works by killing the organisms that cause malaria. This medication is also used to treat certain auto-immune diseases (lupus, rheumatoid arthritis). It belongs to a class of medications known as disease-modifying antirheumatic drugs (DMARDs). It can reduce skin problems in lupus and prevent swelling/pain in arthritis. Hydroxychloroquine is not recommended for coronavirus infection, also known as COVID-19 unless you are enrolled in a study. Talk to your doctor about the risks and benefits.



3.2 PRODUCT IDENTIFICATION

CAS No. (Chemical Abstracts Service)	118-42-3
EC No. (European Community Number)	204-249-8

Molecular Formula C18H26ClN3O
Molecular Weight 335.9 gm/mole
IUPAC Name 2-[4-[(7-chloroquinolin-4- yl) amino] pentyl ethylamino] ethanol

3.3 HYDROXYCHLOROQUINE IS CALLED AS:

2-((4-((7-chloroquinolin-4-yl) amino) pentyl) (ethyl)amino) ethan-1-ol4-Fluorobezene bromide
2-((4-(7-chloroquinolin-4-ylamino) pentyl) (ethyl)amino) ethanol4-Fluoro-1-bromobenzene
2-[{4-[(7-Chlor-4-chinolinyl) amino] pentyl} (ethyl)amino] ethanolp-Fluorophenyl bromide
2-[{4-[(7-Chloro-4-quinoléinyl) amino] pentyl} (éthyl)amino] éthanol4-Bromophenyl fluoride
2- [{4-(7-Chloro-4-quinolinyl) amino] pentyl} (ethyl)amino] ethanol

3.4 HOW WELL DOES IT WORK?

In different regions of the globe, hydroxychloroquine is used to prevent or control malaria and gives current guidelines and travel recommendations for malaria prevention and treatment. This drug is also used to treat some types of auto-immune illnesses (lupus, rheumatoid arthritis). It's one of a group of pharmaceuticals known as disease-modifying antirheumatic drugs (DMARDs). It can help with lupus skin issues and arthritis swelling and discomfort. Unless you're engaged in a trial, hydroxychloroquine isn't suggested for coronavirus infection, commonly known as COVID-19. The application of hydroxychloroquine linoleate in enhancing fluorouracil sensitivity in colorectal cancer is described in the invention. The invention also includes an in-vivo evaluation technique for increasing hydroxychloroquine linoleate's fluorouracil sensitivity in colorectal cancer. The invention pertains to a new application of chloroquine or a derivative hydroxychloroquine medicine, in particular to the application of chloroquine or derivative hydroxychloroquine in medicine for treating Graves eye disease.

IV. PRODUCTION METHOD

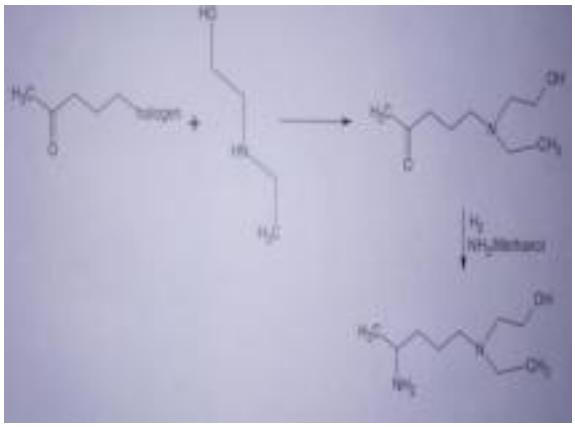
4.1 5-(N-ethyl-N-2-hydroxymethyl amino)-pentylamine (KSM of Hydroxychloroquine) ➢

Process Description:

A 323 g combination of 1-chloro-4-pentanone in 1.3 liters of xylene, 480 g of N-ethyl N-2-hydroxyethyl amine, and 400 g of sodium chloride (to help in subsequent filtering) were heated in a steam bath for two hours with stirring and then refluxed for three hours. The mixture was filtered and the filter cake was washed with Xylene after standing overnight. Fractionally distilling the filtrate yielded 207.3 g of a fraction distilling at 89-90 C at 0.35 mm; m25, 1.4600. (N-ethyl-N-2-hydroxymethyl amino)-4-pentanone is a fraction of (N-ethyl-N-2-hydroxymethyl amino)-4-pentanone. In the following phase of the Synthesis, it was employed. Distillation via a column purified a sample of the aid fraction, yielding an analytically pure sample of 1- (N-ethyl-N-2 – hydroxymethyl amino) – 4pentanone. The above-mentioned 1 (N ethyl-N-2-hydroxymethyl amino)-4-pentanone (284.2 g) was dissolved in 300 g of 28 percent ammoniacal methanol and catalytically reduced at room temperature with Raney nickel (at an initial pressure of 1000 pounds). After 24 hours, the catalyst was removed and the product was distilled in vacuo via a Column, producing 254 g of

a fraction distilling at 88.5-96 °C at 0.3 mm and mostly containing 5- (N-ethyl-N-2-hydroxymethyl amino) -
2 pentylamine. n 25, 1.4703; an analytical sample of this fraction distilled at 93" cat 0.6 mm

➢Chemical reaction



➢7-chloro-diphosphate (Hydroxychloroquine)4(5-(N-ethyl-N-2-hydroxymethyl amino)-2-pentyl) aminoquinoline

➢Process Description:

90 g of 4,7-dichloroquinoline, 90 g of phenol, 1. g of potassium iodide, and 132 g of 5 (N ethyl-N-2-hydroxymethyl amino)-2- pentylamine were heated at 125-130°C for 18 hours with stirring.

V. HOW SAFE IS HYDROXYCHLOROQUINE?

➢Pollution Control

The harmful impact of pharmaceutical product manufacturing on the environment is widely acknowledged. However, because it is mostly uncontrolled, the severely harmful impact it has on both animals and people continues unabated. The chemical hydroxychloroquine presented a long-term hazard to the aquatic ecosystem. This medication is part of a class of quinoline compounds that are poisonous, carcinogenic, and teratogenic.

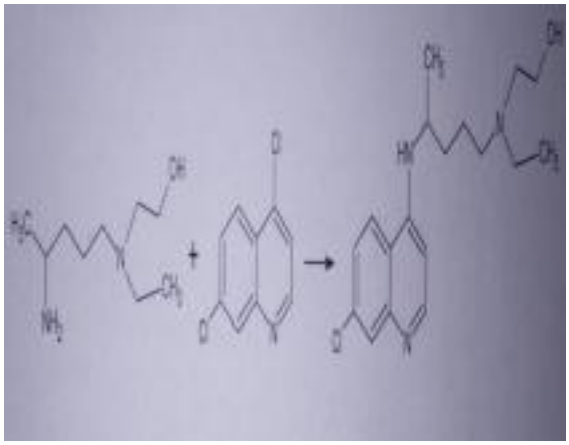
➢Basic Laboratory Safety

To ensure basic laboratory safety, all employees must comply with thefollowing basic steps:

- Quickly clear up all spillages
- Maintain a tidy work area frequently wash hands
- Wear a laboratory coat
- Never smoke inside the laboratory
- Label containers correctly
- Wear eye protection

The mixture was filtered with charcoal after being treated with methanol (3.9 liters). The filter was treated with 270 cc. of a phosphoric acid solution in 300 cc. of methanol, the ways of the flask containing the filtrate were scraped with a glass rod, and the combination was allowed to stand for two days. The material was filtered off, washed with methanol, and dried, producing 101 g of crude -chloro-4-15 (N ethyl-N-2-hydroxyethylanino) -2-pentyl) aminoquinoline diphosphate. Purified 7-chloro-4-5- (N- ethyl- N -2-hydroxymethyl amino)-2-pentyl) aminoquinoline was obtained by recrystallizing this substance from ethylene dichloride or ethyl acetate.

➢Chemical reaction



VI. RISK ASSESSMENT AND HANDLING CHEMICALS

Walk around the work area, checkup possible risks on the HSE website, and look through accident log sheets to see if there are any hazards. 4- 7-dichloroquine, methanol, and xylene are among the dangerous compounds employed in this method. Second, make a note of who could be harmed as a result of any detected hazards. Methanol, for example, is a flammable and dangerous substance. The third phase entails taking action and selecting how to address the risks. The danger must be eliminated or reduced legally. For example, all above-ground storage tanks and fire safety systems must be equipped with a dyke wall to prevent access to the danger or to remove it from the premises as quickly as feasible.

know that dangerous chemicals such as methanol and others are employed in this procedure, therefore we must treat them correctly. Methanol must be stored in pipelines and storage tanks, whereas 4-7-dichloroquine must be stored in begs. Chemical transportation may be extremely hazardous, and if done incorrectly, can result in fires, explosions, and chemical spills. The Handling,

Transport, and Use of Toxic Atmospheres Regulations 2002 stipulate that the risk "shall be as safe as practically practicable," according to the Health and Safety at Work Act.

VII. CONCLUSION

More research into the use of hydroxychloroquine and chloroquine in the prevention and treatment of COVID-19 is urgently needed. Larger controlled trials are needed to more completely investigate if hydroxychloroquine/chloroquine has a clinical benefit in COVID-19, given the little data currently available. In this endeavor, we employ a reaction of 4,7-dichloroquine with 2-amino(5-diethylamino) pentene and other Regal Remedies Ltd. processes to create Hydroxychloroquine. In our patients, HCQ resulted in a considerable reduction in the symptoms of mild to moderate knee osteoarthritis and hence can be recommended for the treatment of knee osteoarthritis.

Acknowledgments

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