ANNQUEST JULY 2020
ISSN:2321-3043

www.stannsannquest.com

BRIEF INSIGHT ON THE PLAUSIBLE SYNTHESIS OF HYDROXYCHLOROQUINE DURING SPREAD OF COVID 19

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Abstract:

Recent spate of novel corona virus (2019-nCoV) also termed as SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) belongs to the corona family has panicked the world, especially the research fraternity. The pandemic was first identified in Wuhan City, China and till now has affected around 215 countries and territories, causing nearly 300,000 deaths within a span of six months. Protective measures were taken to save the lives of patients infected from the virus by providing therapeutic use of Hydroxychloroquine(HCQ) and chloroquine(CQ). HCQ was expected to be potential drug for treatment of nCovid-19. Although, there was no proof of concept that this drug could treat, however, some patients showed exceptional recovery with its use. Hence, the demand in the production of this drug increased subsequently. This paper gives a brief insight of the previous synthetic routes reported for Hydroxychloroquine and chloroquine along with its pharmacology.

Keywords: Covid-19, 4-aminoquinolines, Hydroxychloroquine, Chloroquine.

Introduction:

Chloroquine (CQ) is an antimalarial drug and history of anti-malarials start with quinine, which is active compound in Cinchona bark. The bark contains alkaloids, including quinine and quinidine are part of medicinal chemistry. Chloroquine was synthesized in 1935 by HansAndersag and in 1950 hydroxychloroquine (HCQ) was synthesized. Recently it was found to be effective in the treatment of novel corona virus SARS- CoV- 2 as it inhibits the invitro [1,2] activity of RNA replication. Hydroxychloroquine is the synthetic compound belonging to a class of 4-aminoquinolines, such as chloroquine, amodiaquin whereas less frequently used antimalarial drugs belong to other groups (such as the endoperoxidases (artemisinin) or acridines (mepacrine)) differs from chloroquine by the presence of a hydroxyl group at the end of the side chain: the N-ethyl substituent is β - hydroxylated. HCQ was historically used to treat malaria, especially for the

patients whose immune system cannot withstand the chloroquine. Rheumatoid arthritis is also treated by HCQ. It combats autoimmune diseases such as lupus erythematosus, solar urticaria, and porphyria cutanea tarda , and also as a useful steroid-sparing agents for the treatment of chronic pulmonary sarcoidosis requiring high-dose glucocorticoid therapy [3]. Human coronavirus (HCoV) caused a near pandemic of severe acute respiratory syndrome. Till now no specific antiviral drug for the prevention or treatment of HCoV is available. In current situation the widespread of Covid-19 has explored the potential of this drug for administering to patients, based on previous research where chloroquine has shown in vitro activity against many different viruses like SARS-CoV-1[4], Ebola, MERS, HIV, and influenza [5]. It is recommended that COVID-19 patients can be treated with HCQ-azithromycin to cure infection and reduce the transmission of the virus to curb COVID-19 [6,7].

1.1 Structure of HCQ and CQ:

PLAQUENIL is a commercial name given to hydroxychloroquine sulfate was found successful in confronting the Covid19 virus. HCQ is a white crystalline solid, soluble in universal solvent-water but insoluble in organic solvents such as alcohol, chloroform and in ether. The chemical name for hydroxychloroquine sulfate is 2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl] ethylamino]ethanol sulfate (1:1). Commonly used antimalarial drugs can be divided into different classes on the basis of their core structure. Hydroxychloroquine and chloroquine belong to a class of drugs known as 4 -aminoquinolines, whereas other less frequently used antimalarial drugs belong to other groups such as the endoperoxidases (artemisinin) or acridines (mepacrine) [8] depicts the structure of hydroxychloroquine and chloroquine. Both drugs have a flat aromatic core structure and are weak bases due to the presence of a basic side chain. The basic side chain is thought to contribute to the accumulation of these drugs in intracellular compartments, especially lysosomal compartments, which seems to be crucial for their activity and the potential interaction of these drugs with nucleic acids. Both hydroxychloroquine and chloroquine occur as enantiomers (R and S isomers). (R)- (−) - hydroxychloroquine (the stereochemical 'rectus' configuration of hydroxychloroquine) is present at higher concentrations in the blood than (S)- (+) - hydroxychloroquine (the stereochemical 'sinister' configuration of hydroxychloroquine) [9], suggesting the existence of stereoselective processes in the deposition and/or metabolism of this drug. The efficacy and safety of the drug enantiomers may also differ (Figure 1)

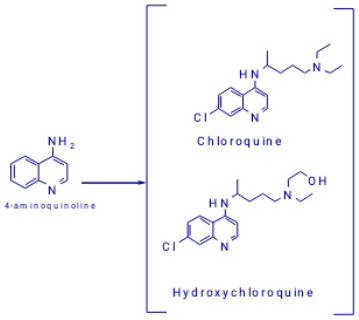


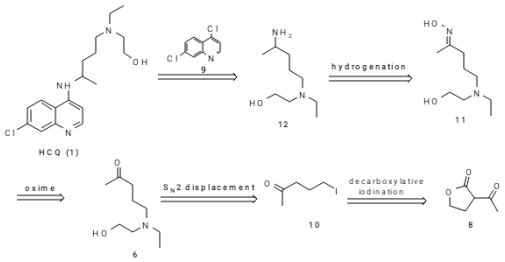
Figure 1: A typical structure of 4-aminoquinolines

2. Recent approaches for the synthesis of HCQ:

2.1. B. Frank Gupton* *et.al* [10] in 2018 has adopted the highly efficient synthesis method for the production of hydroxychloroquine. The process employs a combination of packed bed reactors with continuous stirred tank reactors for the direct conversion of the starting materials to the product. This high-yielding, multigram-scale continuous synthesis provides an opportunity to achieve increase global access to hydroxychloroquine for treatment of malaria.

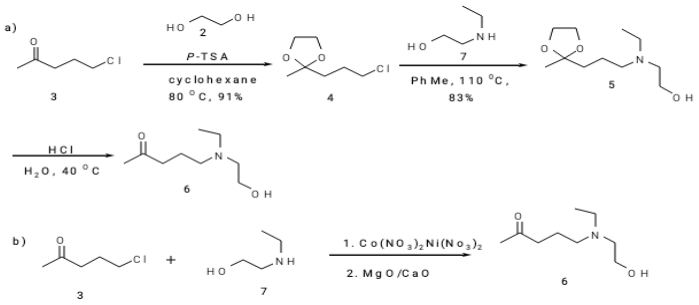
The retrosynthetic route follows the **scheme 1** by the formation of key intermediates **6** and **12**.

Scheme 1



Scheme 1: Retrosynthetic strategy to Hydroxychloroquine (1)

Compound **3** was synthesized from acetyl lactone **8** via decarboxylative reaction. It was subjected to protection of ketone by formation of acetonide **4** with ethylene glycol in the presence of *p*-TSA. Reaction of compound **4** with amino alcohol 7 on heating at temperature 110 ^{O}C in presence of toluene to give the product **5**, followed by acetonide deprotection to give keto-amino alcohol **6**.(**scheme 2a).**
Compound **3** on direct reaction with amino alcohol **7** in the presence of complex Cobalt Nickel nitrito complex and oxide of magnesium or calcium gives compound **6 (scheme 2b).**
Scheme 2



Compound **6** on formation of oxime with hydroxylamine hydrochloride to give compound **11**. Additionally, they have developed and optimized flow-chemistry conditions for performing reductive amination of **11** using Raney-nickel as catalyst in a continuous stirring tank reactor (CSTR) for the synthesis of compound **12**, from lactone **8** and amino ethanol 7. Feeding the output stream containing **12** from the above CSTR into a second CSTR in which **12** is converted to HCQ (1)

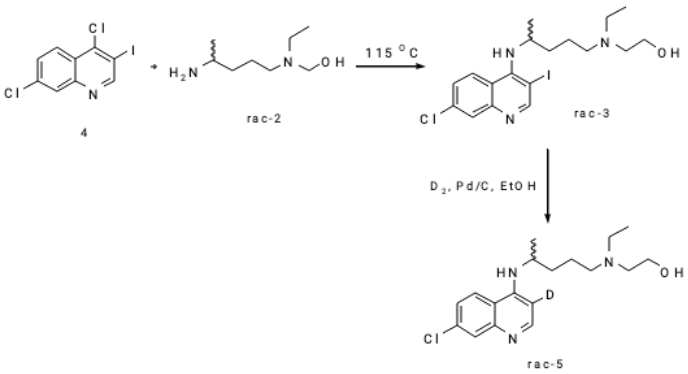
provides a completely continuous-flow process for producing HCQ (**1**) from readily available starting materials. This efficient process has the potential to increase the global access to strategically important antimalarial drug. The team was successful to demonstrate fully integrated continuous -flow process for the synthesis of HCQ (**1**) for commercial operations.

Frank Gupton* ***et.al*** **[10] in 2018** has adopted the flow method for the synthesis of HCQ . The process has the potential to reach the demand of the market. Method has developed major protections, deprotections and oxidation reductions with an inbuilt integrated continuous-flow process by using continuous stirring tank reactor for the direct conversion of the starting materials to the product. The use of Raney Nickle in the process should be handled with utmost care due to chemical sensitivity.

2.2. *George J. Ellames,'J et.al* [11] in the year 1994 has reported the synthesis of enantiomers of [3-3H]-Hydroxychloroquine based on the report that *R*-1 ad *S*-1 enatiomers have different pharmacokinetics in man[7] and different distribution and absorption effects [12,13].

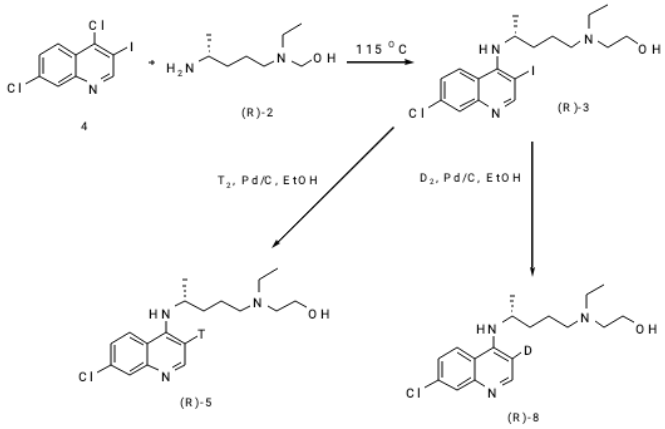
In a preliminary study, 2-[[4-[(7-chloro-3-iodo-4-quinolinyl)amino]penty]ethylamino~ethanol, rac-3, was prepared in 61% yield by treatment of 4,7-dichloro-3-iodoquinoline, 4, [12] with 2-[(4-aminopentyl)ethylamino]ethanol, rac-2.[14] Reductive deiodination of rac-3 at atmospheric pressure, using deuterium over 10% palladium on charcoal in ethanol, afforded the desired [3-2H]-2-[[4-[(7-chloro-4-quinoiinyl)amino]pentyl]ethylamino]ethanol,[3-*H]-hydroxy chloroquine, rac-5, in 68% yield. This sequence is outlined in **scheme 3**.

Scheme 3



Using the enantiomers (R)-2 and (S)-2, the displacements were carried out in diisopropylamine to afford (R)-3 and (S)-3. The enantiomers (R)-3 and (S)-3 gave approximately equal and opposite optical rotations, indicating a lack of significant racemisation at this stage. No racemisation had been observed in the corresponding formation of (R)-1 and (S)-1 described in earlier unlabeled work.9 Reaction of (R)-3 with deuterium, as in the analogous synthesis of rac-5 from rac-3, gave material, (R)-5, with rotation comparable with (R)-1. Additionally, IH NMR revealed no diminution of the signal due to the methine proton gem to the methyl group. From this we concluded that the conversion of (R)-2 to (R)-3 had been achieved without significant racemisation. (**scheme 4)**

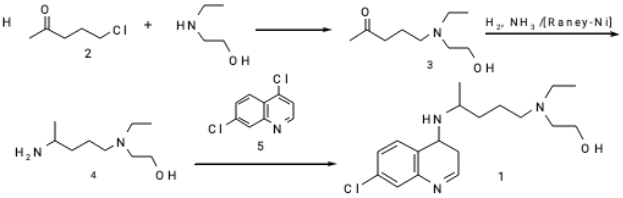
Scheme 4



The above cited method is very much applicable in the asymmetric synthesis and isolates the enantiomers to study different pharmacokinetic studies w.r.t isolation and the synthesis of the product without any further racemisation.

2.3. In **2006**, Vardanayan proposed the synthetic route for the Hydroxychloroquine*:* [15] 7-chloro-4-[4-[ethyl(2-hydroxyethyl)amino]- 1-methylbutylamino]quinoline **1**, is synthesized as per the **scheme 5.** Reacting 1-chloro-4-pentanone **2** with 2-ethylaminoethanol gives the corresponding aminoketone **3**, which undergoes reductive amination, making 4-[ethyl(2-hydroxyethyl)amino]-1-methyl butylamine **4**. Reacting this with 4,7-dichloroquinoline **5** makes the desired hydroxychloroquine **1** [16,17].
Hydroxychloroquine, like chloroquine, is also used for treating acute forms of malaria caused by *P. vivax, P. malariae, P. ovale*, and also sensitive forms of *P. falciparum.* It is also effective and safe like chloroquine, although it does not have obvious advantages. The only advantage is that it is somewhat better tolerated. Its use is somewhat more limited than chloroquine. Synonyms of this drug are plaquenil, quensyl, toremonil, and others.

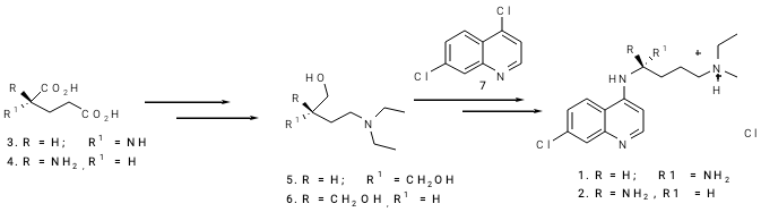
Scheme 5:



Vardanayan scheme shows a simpler methodology applied in the scheme such as substitution, hydrogenation etc. The HCQ was emphasized to be a better tolerant in the treatment as a pharmacological agent.

2.4. Witiak et. al [18] synthesized asymmetric chloroquine analogues with its pharmacological evaluation. Optically pure analogues 1-2 of known absolute configuration were prepared from (*S*)- or (*R*)-glutamic acid (**3 or 4**) **(scheme 6)** *via* intermediates **5** and **6**, respectively. Hydrophylic HO-substituted chloroquine enantiomers **3** and **4** were obtained via condensation of **5** and **6**, respectively, with 4,7-dichloroquinoline **7.**

Scheme 6

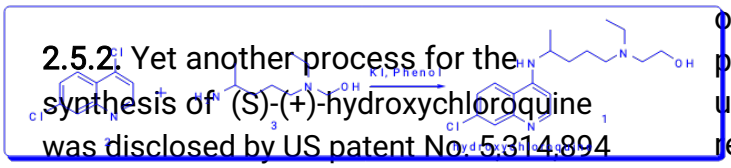


The above scheme provides the synthesis favoring the asymmetric route.

2.5. Patents related to the new synthesis of Hydroxychloroquine:

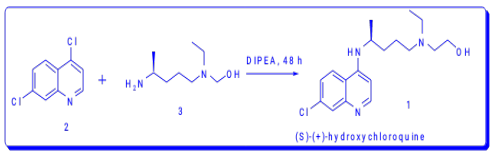
2.5.1.The preparation of HCQ was first disclosed in US patent No. 2,546,658. It includes a process for preparing hydroxychloroquine diphosphate **1**, which involves reacting 4,7-dichloroquinoline of the following formula **2** with N'-ethyl-N'- β-hydroxyethyl-l,4-pentadiamine of the following formula **3** in the presence of potassium iodide (KI) and phenol at a temperature of 125 to 130 ^{O}C 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% **(scheme 7).**

Scheme 7



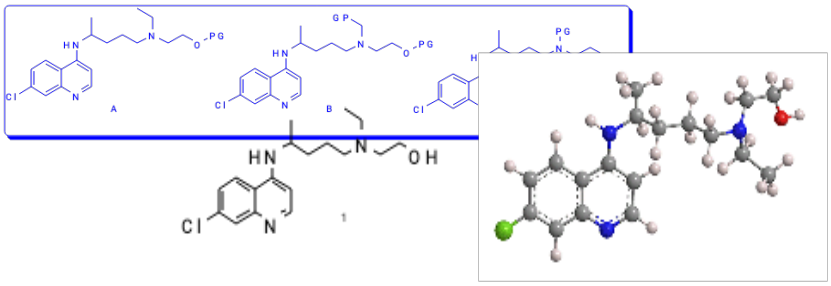
2.5.2. Yet another process for the synthesis of (S)-(+)-hydroxychloroquine was disclosed by US patent No. 5,314,894 for the synthesis of (S)-(+)-hydroxychloroquine **1** wherein 4,7-dichloroquinoline **2** and (S)-N-ethyl-N'- ®-hydroxyethyl-l,4-pentadiamine **3** with N,N-diisopropylethylamine (b.p 127 ^{O}C were heated at reflux for 48 hours to obtain with a yield of 46% (**scheme 8).**

Scheme 8



2.5.3. 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-l,4-pentadiamine **3** at a temperature of 120-130 ^{O}C at a temperature of 120-130 ^{O}C for 20 -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 (**scheme 9**).to obtain a desired product hydroxychloroquine.

Scheme 9



HYDROXYCHLOROQUINE

With current 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 phenolora reagent such as N,N-diisopropylethylamine,which has a high boiling point and a structure similar to that of the final product. Particularly, along 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.

2.5.4. The present invention (WO2010/027150A2) [19] 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.

The process is carried out as follows. First, 4,7-dichloroquinoline and N'-ethyl-N'-ß-hydroxyethyl-l,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 ^{O}C for 30 min until 4,7-dichloroquinoline is completely dissolved, followed by further stirring at a temperature of 100 to 120 ^{O}C for 4 to 6 hours.

With regard to the US patents explained under **scheme 2.5** different conditions were employed for a better selectivity and yields of the product
The efficacy of the HCQ is under study for the treatment COVID 19 by different organizations including commercial establishments throughout the world. No pharmacological agent has been approved by regulatory agencies for the treatment of SARS-COv-2. Still many believed that CQ and HCQ may be the potential drug for the treatment of COVID-19 .

As per press release dated May 14, 2020 by *NIH*, NIH (National institute of Health), NIAID (National Institute of Allergy and Infectious Diseases) and Teva Pharmaceuticals (which is donating medications) have collaborated in conducting the trials for the study, they further stated that there is a need for clinical data to use Hydroxychloroquine and Azithromycin in combination to develop more quickly and move to the clinical trials.

Indian Express Dated May 27, 2020, published an article which stated HCQ is India's drug of choice both for treatment and prophylaxis (post-exposure preventive). India has been exporting it to 55 countries such as France, Brazil, Russia, and South Korea.

According to ICMR, a report published in the *India Today* dated June 1st 2020, "a sustained intake of anti-malarial drug hydroxychloroquine (HCQ) has shown positive results in reducing the risk of corona virus in the health care workers, HCQ prophylaxis should be taken in tandem with wearing the personal protective equipment (PPE) to minimize risk exposure."

HCQ has invitro efficacy against SARS-CoV-2(Wanger *et.al* 2020) and some preliminary efficacy against COVID-19(Gao.*et.al* 2020) .Multiple trials targeting different populations world-wide using a range of doses as well as outcomes have already been registered to date. CQ and its derivatives have shown early promise to treat COVID-19 and should be explored as a potential drug in this rapidly evolving pandemic.

CQ and its derivatives show early promise to treat SARS-CoV-2 and should be explored as a potential preventive and therapeutic measure to turn the tide of this rapidly growing pandemic by Kearmey.J "chloroquine as a potential treatment and prevention,measure for the 2019."

Yet there is no proven evidence for

assessing systematic trials that address the preventive efficacy of CQ and HCQ against COVID-19. Though HCQ is used in various viral infections, but very limited information available to summarize the evidences about the role of HCQ in treatment of Corona Virus. Clinical trials are going on using CQ and HCQ in COVID-19 infection are quite promising.

Conclusion: Overall, this paper is a review of various synthetic methods adopted previously for hydroxychloroquine drug. Since, the demand of this specific drug has increased tremendously due to on spread pandemic nCovid-19 globally, this review gives insights in production of it.

Acknowledgment: The authors acknowledge St.Ann's college for Women-Mehdipatnam, for providing the platform and opportunity.

Competing interests: None declared.

Ethical approval: Not required.

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