The Rise and Fall of Hydroxychloroquine (HCQ) in COVID Era: A Therapeutic Journey and Synthetic Progress

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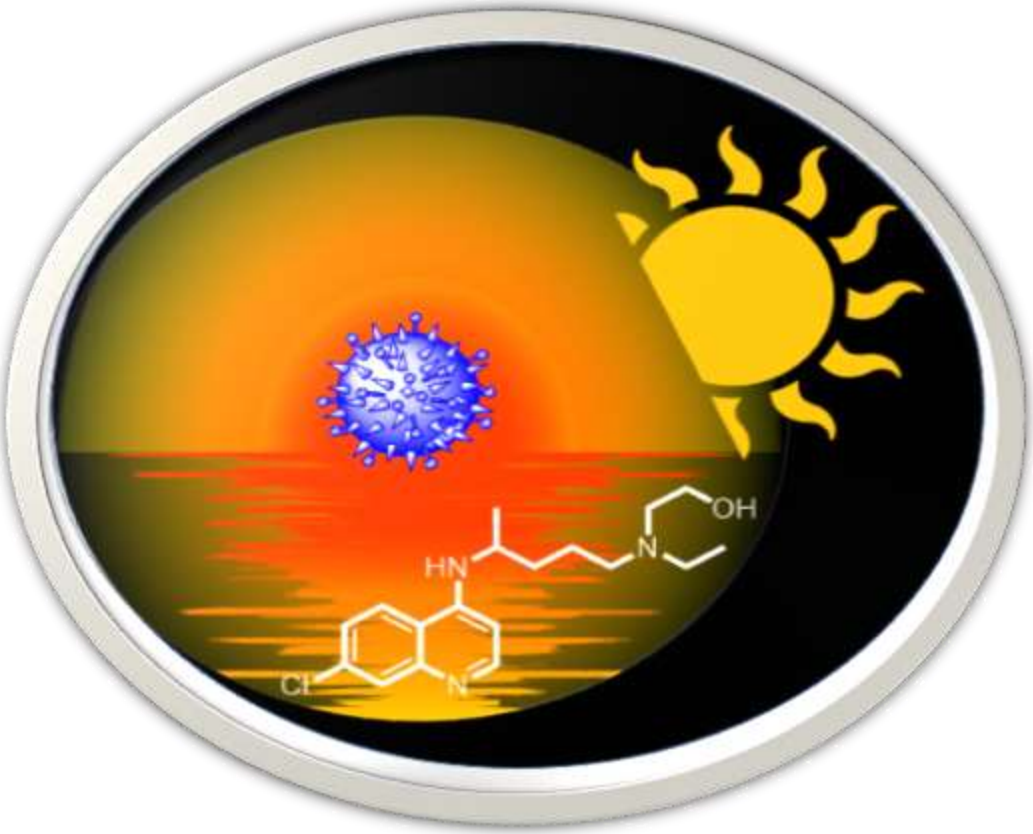
Graphical Abstract



Keywords: Coronavirus disease-19 • Drug repurposing • Hydroxychloroquine • Emergency Use Authorization • Synthesis

Abstract: With no proven therapy against COVID-19, the repurposing of existing drugs is an ongoing exercise. In this context, an antimalarial drug, hydroxychloroquine (HCQ) received immediate stardom when the US-FDA issued an Emergency Use Authorization (EUA) for HCQ against COVID-19 based on the limited clinical study. However, on 17 June 2020, WHO announced the stoppage of HCQ trial for COVID-19 treatment based on data received from Solidarity trial and UK's Recovery trials indicating HCQ does not result in the reduction of mortality of hospitalized COVID-19 patients when compared with standard of care. In this context, the present review aims to provide a developmental journey of HCQ including medicinal chemistry highlighting the essential pharmacology and the current studies exploring its effectiveness against COVID-19, and its synthetic advancement.

1. Introduction

What initially started as infectious respiratory symptoms in the Wuhan region of China, turned out a globally acclaimed pandemic known as Coronavirus Disease-2019 (COVID-19).[1] It is caused by a coronavirus, 2019-nCoV, known as severe acute respiratory syndrome-related coronavirus SARS-CoV-2.[2] As of May 15, 2020, more than 4,494,873 confirmed cases and over 305,976 confirmed deaths were recorded worldwide spanning to more than 216 countries or territories (Figure 1).[3] Additionally, people's lives around the globe have suffered as a consequence of compulsory quarantines/isolations/restrictions. The worldwide upshot of the COVID-19 pandemic could possibly bring key tasks to healthcare systems and have across-the-board consequences on economics globally.[4]

The coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae, are relatively large with genome size 26 to 32 kilobases, having helical symmetry nucleocapsid with a positive-sense single-stranded RNA genome.[5] The viral capsid is studded with distinctive glycoprotein spikes, which in electron micrographs generate an image expressive of the solar corona, from which their name derives (Figure 2).[6,7,8,9,10] The glycosylated spike (S) protein (structural protein) mediates the host cell entry via binding to a protein (receptor)known as angiotensin-converting enzyme 2 (ACE2) positioned on the surface membrane of host cells primed by the host serine protease TMPRSS211.[11] This interface communication between ACE2 receptor and viral S protein is of high value since it recruits the infection process.[7]

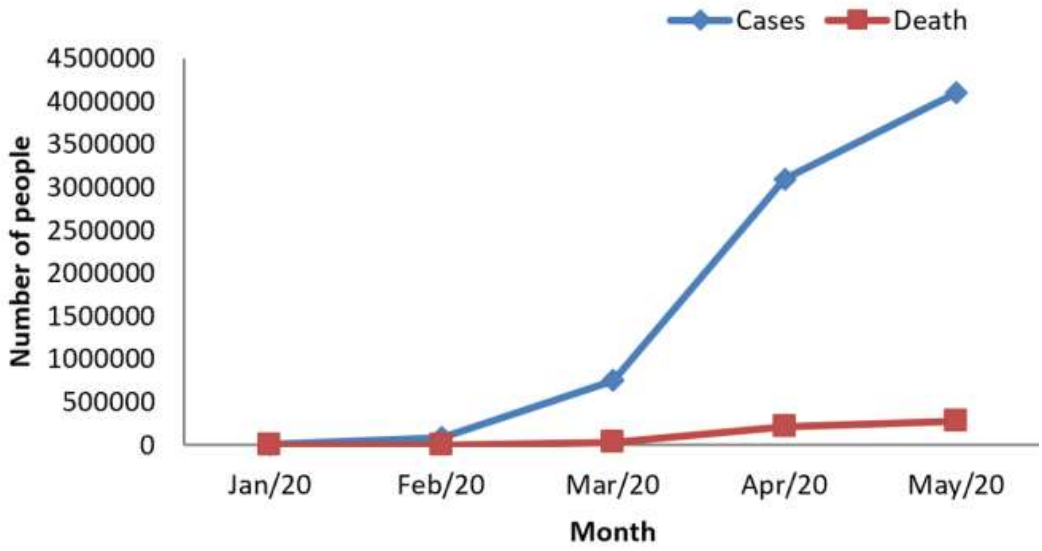


Figure 1. WHO statistics affecting global COVID-19 incidence (till 13th May 2020)

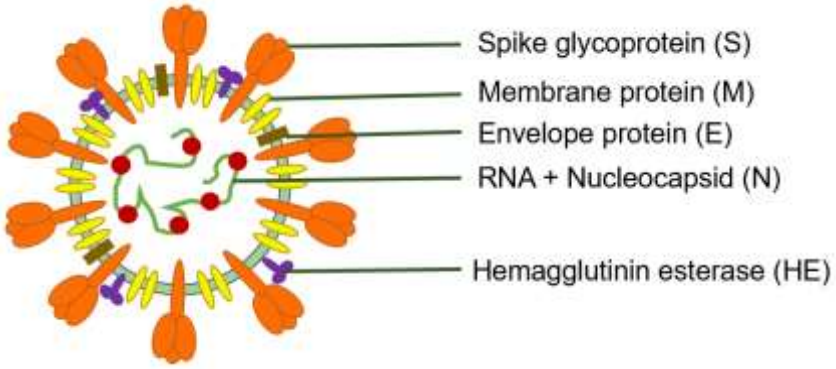


Figure 2. Cartoon representation of the structural of SARS-CoV 2 virion.

Upon entry, they released the viral genome (single-stranded positive RNA) into host cells. Afterward, the viral polyproteins are translated using host cell translation machinery followed by cleavage into effector proteins by viral proteinases, coronavirus main protease (3CLpro), and papain-like protease (PLpro).[9,10,11,12] Subsequently, viral RNA-dependent RNA polymerase (RdRp), catalyzes the synthesis of a full-length negative-strand RNA template to be utilized to construct more viral genomic RNA.[13,14]

Such critical and pandemic situation demands immediate therapeutic rescue; however, no proven therapy has been established so far.[15] This causes a shift in the policy "from drug discovery to drug repurposing" where clinically proven drugs are reutilized for new indications.[16] In this course, *in vitro* or *in silico* drug screening tool identified few FDA-approved drugs as a possible treatment for COVID-19. Towards this end, chloroquine or hydroxychloroquine (debatable), lopinavir/ritonavir, and favilavir were promising candidates and are in clinical trials for the treatment of SARS-CoV-2.[17,18]

2. Historic development of HCQ

The historical development of HCQ started way back in 1630's when quinine was first used by Incan descendent in Peru as a traditional way to treat febrile illness from a powder of mystic, the bark of miracle tree which was later (1742) named as cinchona (*Cinchona officinalis*) by Linnaeus.[19] Later on, in 1820, it was isolated from the cinchona bark by a French chemist, and quinine became a reference treatment for sporadic fever all over the world.[20] In 1930, a related molecule, quinacrine was introduced for the treatment of malaria, however, it was found highly toxic and also inferior compared to quinine. In order to discover an alternative to quinine, in 1934, Hans Andersag and coworkers at the Bayer laboratories synthesized the chloroquine (CQ) and named as Resochin.[21] Later on, CQ was established as a promising antimalarial drug following the US government-sponsored clinical trials

under the antimalarial drug development program.[22,23] Following world war II, CQ and DDT emerged as the two key arms in WHO's global eradication malaria drive. Subsequently, CQ was also found effective in reducing rashes and inflammation (immune suppression) which ultimately led to CQ as an effective medicine for autoimmune disorders, such as rheumatoid arthritis and lupus erythematosus. In the year 1955, a water-soluble hydroxyl-containing chloroquine derivative as hydroxychloroquine (HCQ; **1**) was approved by US FDA for the treatment of malarial fever (Figure 3).[24] It is a racemic mixture consisting of an (*R*) and (*S*) enantiomer, and currently sold under the brand name of Plaquenil®, Hydroquin®, Axemal®, Dolquine®, Quensyl®, Quinoric®, etc. as a therapeutics for malaria, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and primary Sjögren syndrome.[25,26] Currently, it is one of the frequently prescribed drugs across the USA,[27] and included in the World Health Organization's List of Essential Medicines.[28]

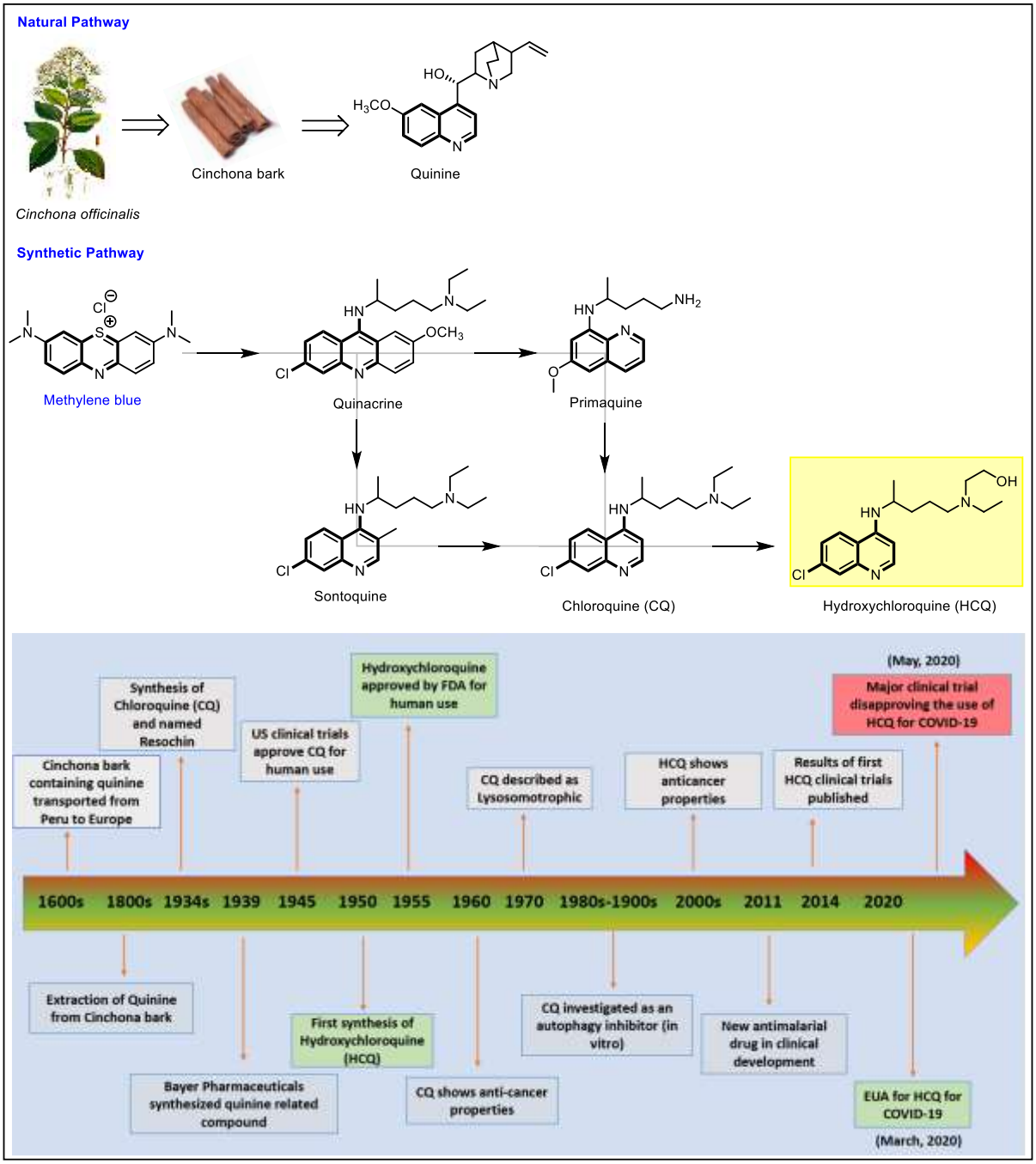


Figure 3. Key events in the discovery of hydroxychloroquine (HCQ)

3. Basic medicinal chemistry of HCQ

HCQ is a lipophilic and weak diprotic basic molecule that passes easily through cellular membranes. The resulting HCQ (free base) accumulates in lysosomes (acidic cellular vesicles), gets protonated, resulting in increased concentrations within lysosomes of the malaria parasite.[29] The increased lysosomal pH interferes with the proteolytic activity of hemoglobin thus preventing the growth of the

parasite.[30] HCQ is also known to affect with the action of parasitic heme polymerase, resulting in the build-up of the toxic β–hematin and kills the parasite (Figure 4).[31,32]

In a similar fashion, HCQ accumulates in human organelles, increase their pH, which averts the dimerization of α and β chains of the major histocompatibility complex (MHC) class II, prevents antigen presentation of the cell,

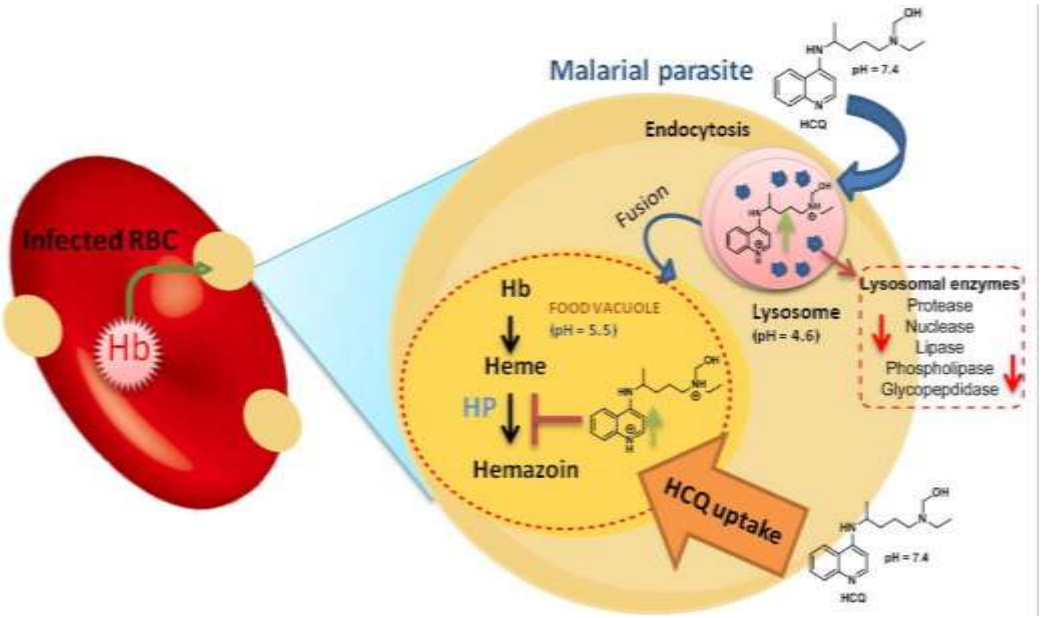


Figure 4. Anti-malarial mechanism of action of HCQ

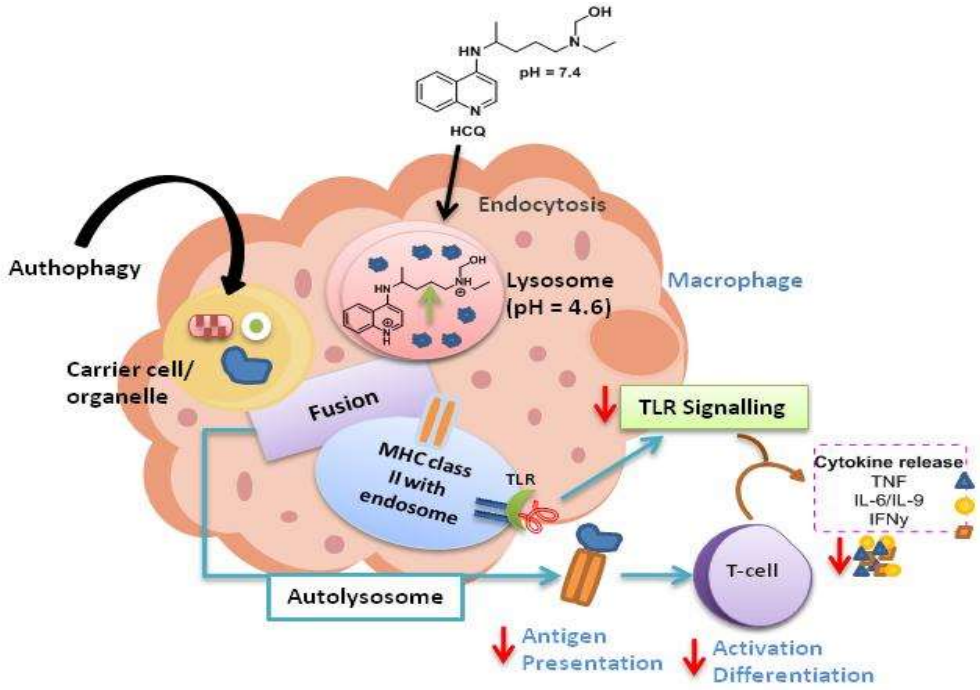


Figure 5. Immunomodulatory mechanism of action of HCQ

and decreases the inflammatory response.[33] HCQ is also known to reduce the release of inflammatory cytokines like tumor necrosis factor (TNF) and interleukin-□. A recent study has shown that during inflammatory conditions, HCQ reduces toll-like receptors (TLR) signalling, decreasing the activation of dendritic cells and the inflammatory process (Figure 5).[34] Thus, HCQ in addition to its anti-malarial properties, modulates autoimmune responses and express anti-inflammatory action at both molecular and cellular level via lysosomal inactivity membrane destabilization, and altered signalling pathways. These actions in-turn also responsible for the adverse effect of HCQ under long-run treatment.

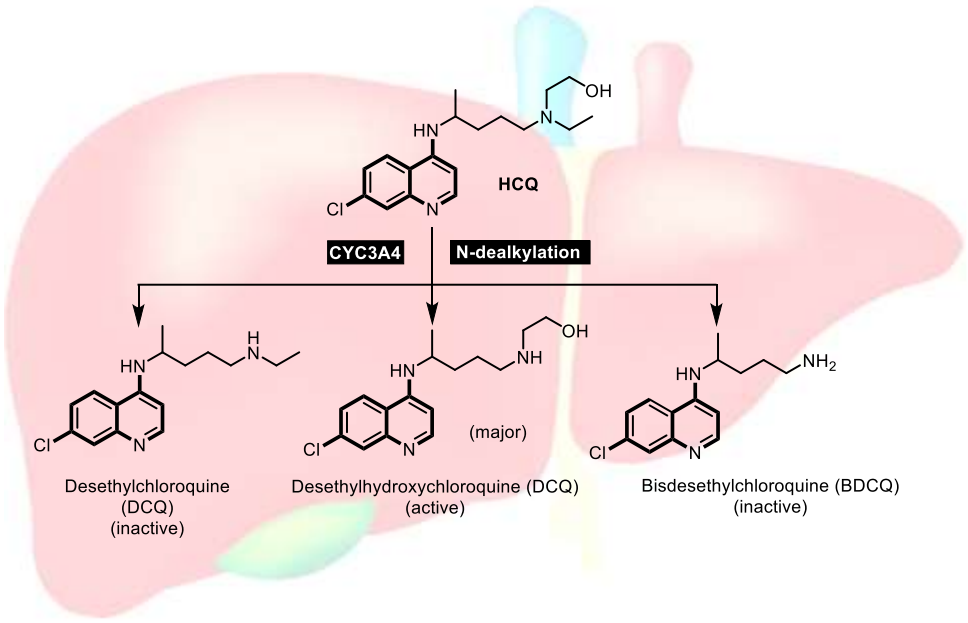


Figure 6. Immunomodulatory mechanism of action of HCQ

HCQ (R/S enantiomers) is rapidly absorbed through the gastrointestinal track with 67-74% bioavailability. It reaches its peak serum level in 2-3.5 hours. It has large distribution volume (V_D = 5522L from blood and 44,257L from plasma) with 45 – 50% protein binding.[35] It metabolized in the liver via *N*-dealkylated catalyzed by CYP3A4 (Figure 6) and mostly eliminated through the kidney (elimination half-life 32-50 days) with clearance rate is 96 mL/min.[36,37]

The common adverse effects are nausea, stomach cramps, and diarrhea. The chronic use of HCQ adversely resulting in dose-dependent retinopathy (eye), hepatotoxicity (liver), anemia, hearing loss, psoriasis, etc.[38,39] HCQ overdose may cause additional cardiovascular collapse, convulsions, and hypokalaemia, etc. which may lead to cardiac arrest and death. Such conditions should be treated with instant gastric lavage and activated charcoal along with parenteral diazepam to treat cardiotoxicity.[38] If taken concurrently, arrhythmogenic drugs, and drugs known for QT prolongation can interact with

HCQ and increases the risk of induced ventricular arrhythmias.[40,41] An utmost care should be taken by pregnant women or nursing mothers.[42]

4. HCQ under Study for COVID-19

With no proven medicine or vaccine to treat or eradicate COVID-19 pandemic, repurposing the existing drugs are promising alternative.[15,16],[17,18] Currently, there are multiple clinically proven FDA approved drugs are in preclinical studies or various phases of clinical trials.[20,21,43,44,45] These include but not limited to CQ (anti-malarial), HCQ (anti-malarial), azithromycin (antibiotic), remedisivir (anti-viral), lopinavir (anti-viral), ritonavir (anti-viral), etc (Figure 3).In this context, HCQ got immediate stardom in mid-March when US President Donald Trump labeled it as a game-changer for the COVID-19 treatment. Whatever it takes, HCQ holds a special position owing to its dual role as prophylactics and therapeutics. Based on the limited clinical study, on 28 March 2020, the US-FDA issued an Emergency Use Authorization (EUA) for chloroquine phosphate and hydroxychloroquine sulfate for the COVID-19 treatment (Figure 7).[46] [46] This inspired the different organizations to start further study and clinical trials in order to validate or establish HCQ (alone or in combination) to combat COVID-19.[47],[48],[49] (see the ESI for the detailed summary of various trials done for HCQ). In this context, the recent study using SARS-CoV-2–infected Vero cells and physiologically based pharmacokinetic (PBPK) modeling shown that HCQ (EC50 = 0.72 μM) possesses a better anti-viral effect than CQ (EC50= 5.47 μM) against SARS-CoV-2 in vitro.[47]

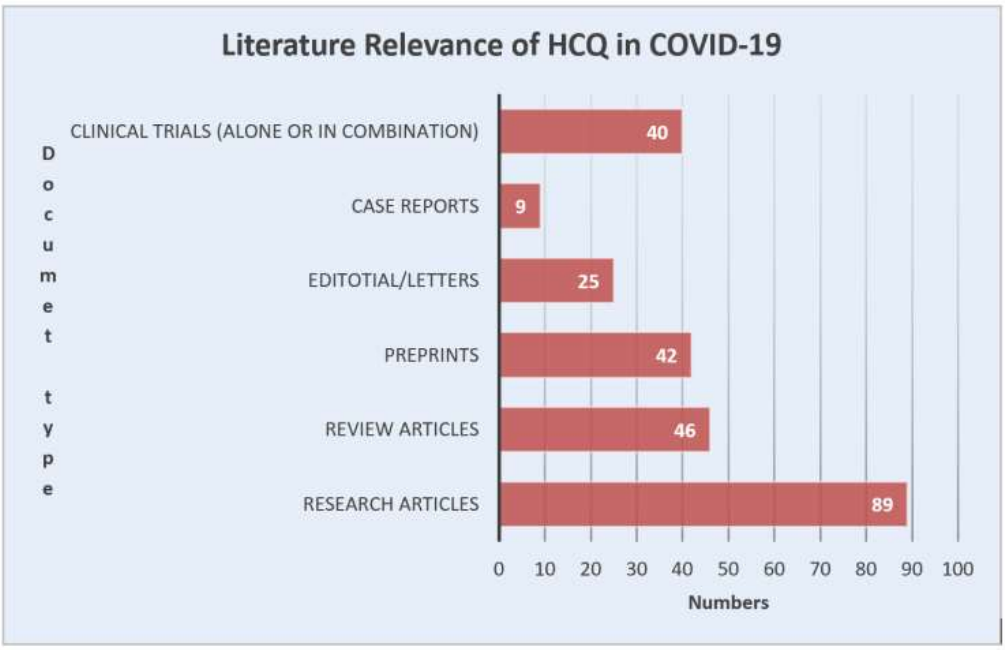


Figure 7. Relevance of HCQ in COVID-19 research. (Source: SciFinder; May 16, 2020)

In India, the Indian Council of Medical Research (ICMR) also recommended the use of HCQ for prophylaxis of all healthcare personnel engaged in the treatment of suspected or confirmed COVID-19 cases with a dose of 400 mg twice daily on day1 followed by 400 mg once weekly for the next 7 weeks to be taken with meals.[48] Meanwhile, various national and international agencies are constantly updating treatment guidelines using HCQ for COVID-19 infection while others are working on drug delivery aspects of HCQ.[49,50,51] In this direction, Manning, and co-workers published the future possibilities of HCQ delivery via vaporization to have a direct therapeutic effect with site-specific action using the nasal route.[52] Interestingly, the aerosol component consisted of the ingredients having either mild to prominent anti-viral or disinfectant property.

Recent findings including molecular modeling studies revealed the significant HCQ mechanistic patterns against SARS-CoV-2. Although it is not clear; the following mechanism has been postulated for the anti-COVID action of HCQ (CQ) affecting inhibition of the viral entry into the host cell and/or the late-stage replications of viral genome (Figure 8). (i) HCQ prevents ACE-2 receptor-mediated viral entry into the host cells. Such a process is initiated by the binding of S-glycoprotein of the virus to sialic acid present of the cell surface (ACE-2 receptor) and primed by a host serine protease (TMPRSS2). Once the virus binds to ACE-2receptor viaS-glycoprotein, it initiates endocytosis mediated cell entry. HCQ prevents the terminal glycosylation (resulting in more expression of sialic acid) of ACE-2 making the interaction with S-protein insignificant. The non-glycosylated (poorly expressed sialic acid) state of ACE-2 receptor does not interact significantly with the S-protein of the virus, decreasing its binding affinity and disbanding the virus-host cell union.[51,53,54,55,56] (ii) After the endo-lysosomal entry of SARS-CoV-2, its spike protein must be cleaved to favor conformational changes required for the fusion of viral envelope with the host cell membrane. This process is primed by host proteases such as serine protease (TMPRSS2) or host cell-derived S-protein.It is assumed that increased pH due to HCQ accumulation resulting in the degradation of pH-sensitive proteases. Thus, HCQ disrupts the pH mediated further transport of viral envelopes.[11,52] (iii) HCQ also acts as Zn^{+2} ionophore resulting in increased Zn^{+2} concentration in the host cell's cytoplasm. Such high Zn^{+2} concentration interferes with the catalytic activity of RNA dependent viral RNA polymerase (RdRP) enzyme and prevents the RNA polymerization.[57,58,59]

The various molecular interactions between HCQ and viral RNA polymerase are reported recently. The -Cl & -OH group of HCQ binds with phosphate's of uracil and adenine respectively via ionic interaction. The -NH group of HCQ forms intermolecular hydrogen bonding with the oxygen of uracil. The aromatic ring of HCQ ensures the effective positioning favoring these binding with the RNA of SARS-CoV-2. With reference to an additional OH-group present in HCQ over CQ, its significance

towards the interaction with RNA of SARS-CoV-2 is evident. Also, these actions of HCQ is aided by the combination of azithromycin, where ionic coupling agents like Mg^{2+}, Ca^{2+}, and Zn^{2+} are involved.[60]

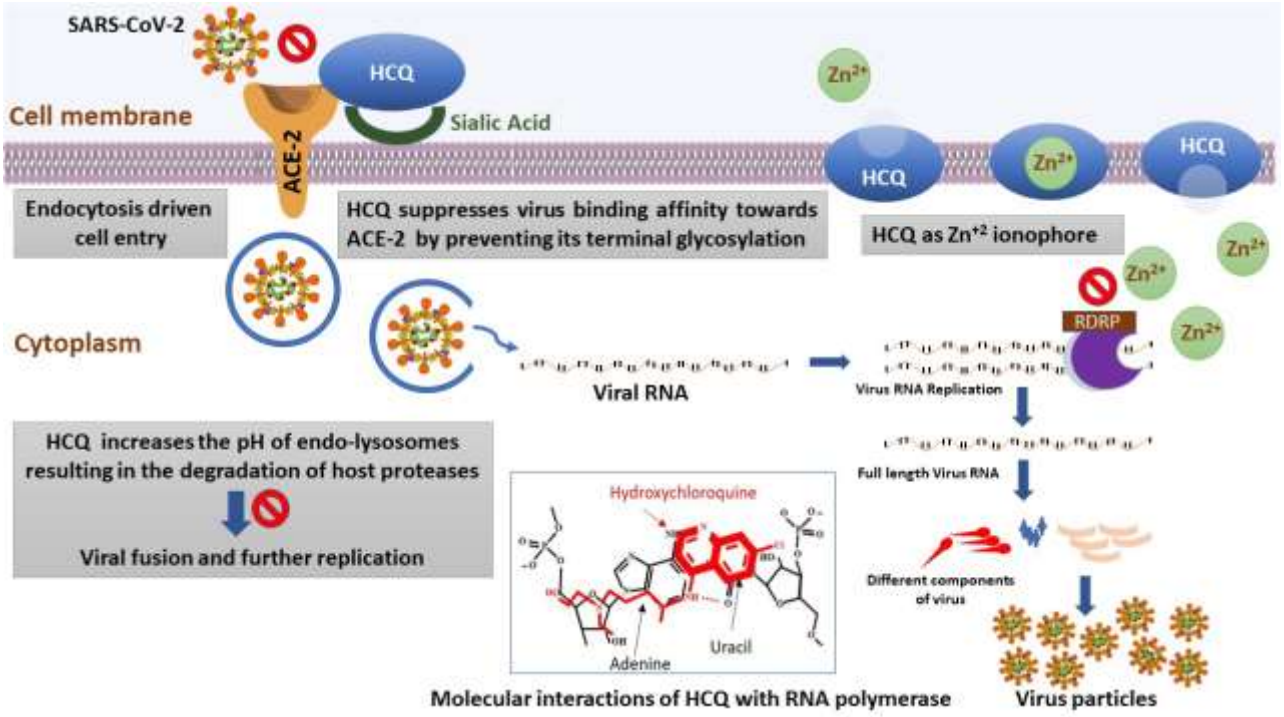


Figure 8. Proposed anti-COVID-19 mechanism of HCQ

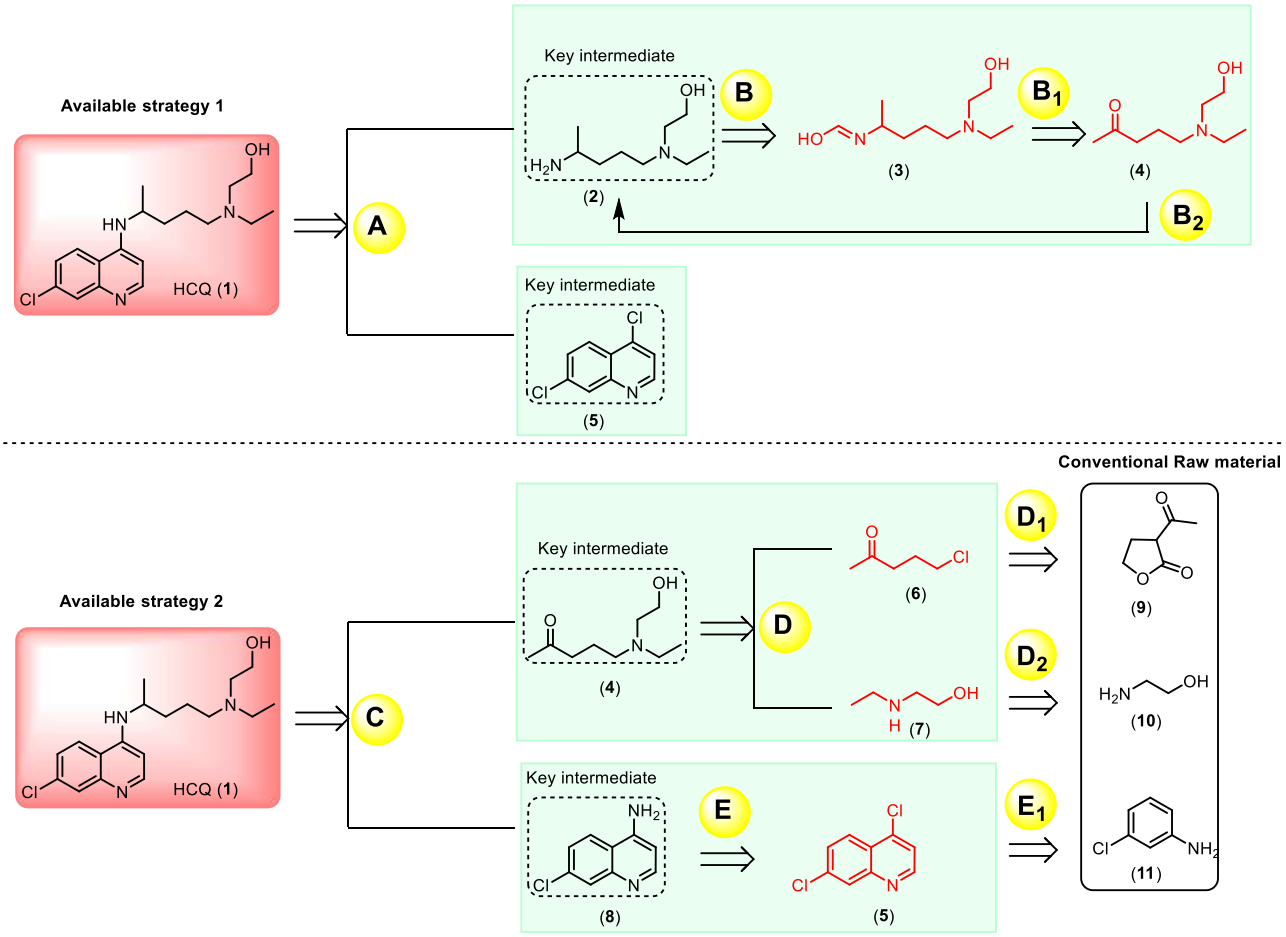
Amidst the beneficial role of HCQ in combating COVID-19, recent exploration of combinational approaches via co-administration of HCQ with azithromycin has gained attention. [61,62,60] However, the given studies had a limitation and did not comment on the adverse effect of QT prolongation. In this regard, Mercuro *et al.* showed a cohort clinical observation of QT prolongation among 90 patients having COVID-19 infection along with comorbidities like hypertension and diabetes mellitus after hydroxychloroquine and azithromycin intake.[63] Such report makes it necessary to understand the risk to benefit assessment of co-administration of this combination for patients suffering from conformities especially with cardiovascular diseases.[64,65] In a similar manner, ivermectin has been recently undergoing examination in combination with HCQ for COVID-19 as it acts synergistically with HCQ.[66,67,68,69]

Choo *et al.* in their report suggested the severity of disease due to non-availability of appropriate medication(s) apart from protective kits (measures).[70] A huge shortage of HCQ has been observed owing to its high global attention across government agencies, healthcare professionals, patients, and the general public in the context of COVID-19 pandemic. Consequently, its misuse and overdose in COVID-19 patients and compromised (restricted) use in patients with rheumatoid and autoimmune

disorders has been observed. Under such circumstances, the government bodies, and healthcare professionals must come up together in controlling the judicial and systematic use of HCQ for COVID-19 with proper emphasis on the urgency of evaluation of HCQ (CQ) to get more relevant clinical data showing the significance of HCQ (CQ) for the COVID-19 treatment.[71,72,73,74] In this regards, amidst of ongoing therapeutic assessment of HCQ, the latest results published in Lancet (May 22, 2020) has shaken the proposed utility of HCQ for COVID-19 treatment.[75] In a statistically significant, large scale study, Dr. Mandeep and *et al.* ruled out any benefits of HCQ (and CQ) for COVID-19 patients. The study further suggests that the use of these two medicines either alone or in combination with macrolides (azithromycin) essentially increases the incidence of heart complications and related death among such patients. The obtained results are the outcome of the data analysis of 96,032 patients hospitalized with laboratory-confirmed COVID-19 infection from 671 hospitals. It has been suggested that such drug treatments should not be recommended to treat COVID-19 patients outside of clinical trials and urgent validation from randomized clinical trials are needed. This study seriously put a break on the possible therapeutic use of HCQ (or CQ) and related study, however, as suggested urgent validation from randomized clinical trials across the globe is the need of hour. Contrary to this, on May 26, 2020, the top medical body of India (ICMR) stated that no major side-effects of HCQ have noted and its use should be continued as preventive care for COVID-19. Subsequently, on June 5, 2020, the Lancet paper that paused global clinical trials of HCQ for COVID-19 has been retracted after a Guardian investigation found inconsistencies in the data that was provided for the research by the US company Surgisphere. Recently, on 17 June 2020, WHO announced that the HCQ arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped. The decision is based on evidence from the Solidarity trial, UK's Recovery trial and a Cochrane review of other evidence on hydroxychloroquine which claims that HCQ does not result in the reduction of mortality of hospitalized COVID-19 patients, when compared with standard of care. However, WHO clearly mentioned that the decision to stop hydroxychloroquine's use in the Solidarity trial does not apply to the use or evaluation of hydroxychloroquine in pre- or post-exposure prophylaxis in patients exposed to COVID-19.

5. Synthetic developments and progress

Analysis of the reported protocols for the synthesis of HCQ **1** (IUPAC name: 2-((4-((7-chloroquinolin-4-yl)amino)pentyl)(ethyl)amino)ethan-1-ol) indicated two common strategies (Schemes 1).The first approach, commonly employed at industrially scale, involves the C-N bond-forming reaction between 2-((4-aminopentyl)(ethyl)amino)ethan-1-ol (**2**) and 4,7-dichloroquinoline (**5**) (Strategy 1; Scheme 1). In second approach, 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (**4**) reacts with 7-chloroquinolin-4-amine (**8**) to give HCQ (**1**) (Strategy 2; Scheme 1).



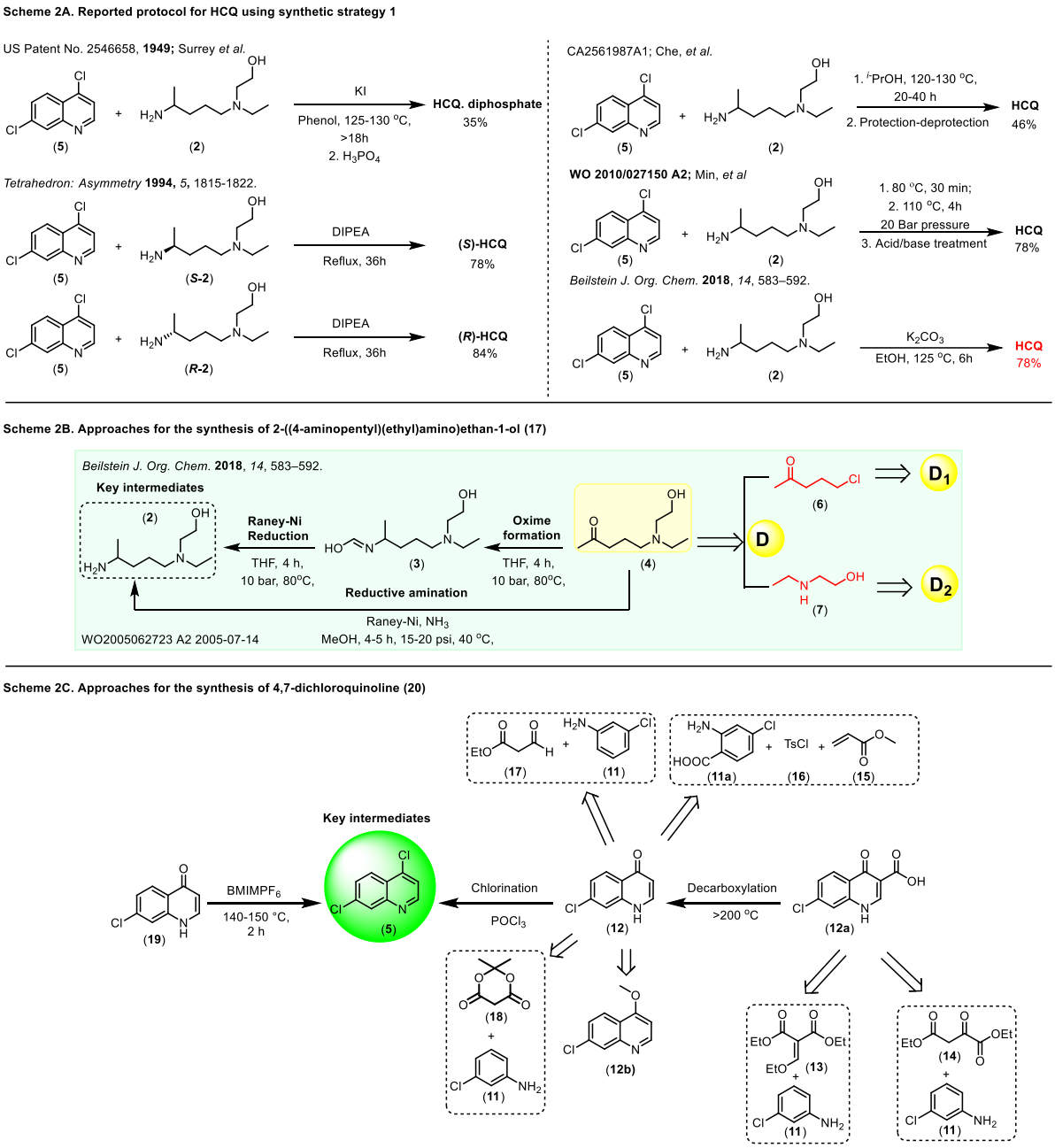
Scheme 1. Retrosynthetic analysis for the HCQ synthesis

Adopting the first synthetic strategy, Surrey *et al.* in the year 1949 reported the first industrial scale protocol for the HCQ synthesis which is still under active use.[76] However, this 3-step protocol offers a 35% overall yield and utilises phenol as solvent (requires significant handling care). Following similar approach, Blanley *et al.*[77] reported the first multi-gram scale asymmetric synthesis of (*R*) and (*S*) enantiomers of HCQ involving chiral resolution of **2** using enantiopure mandelic acid. Chen *et al.*[78]

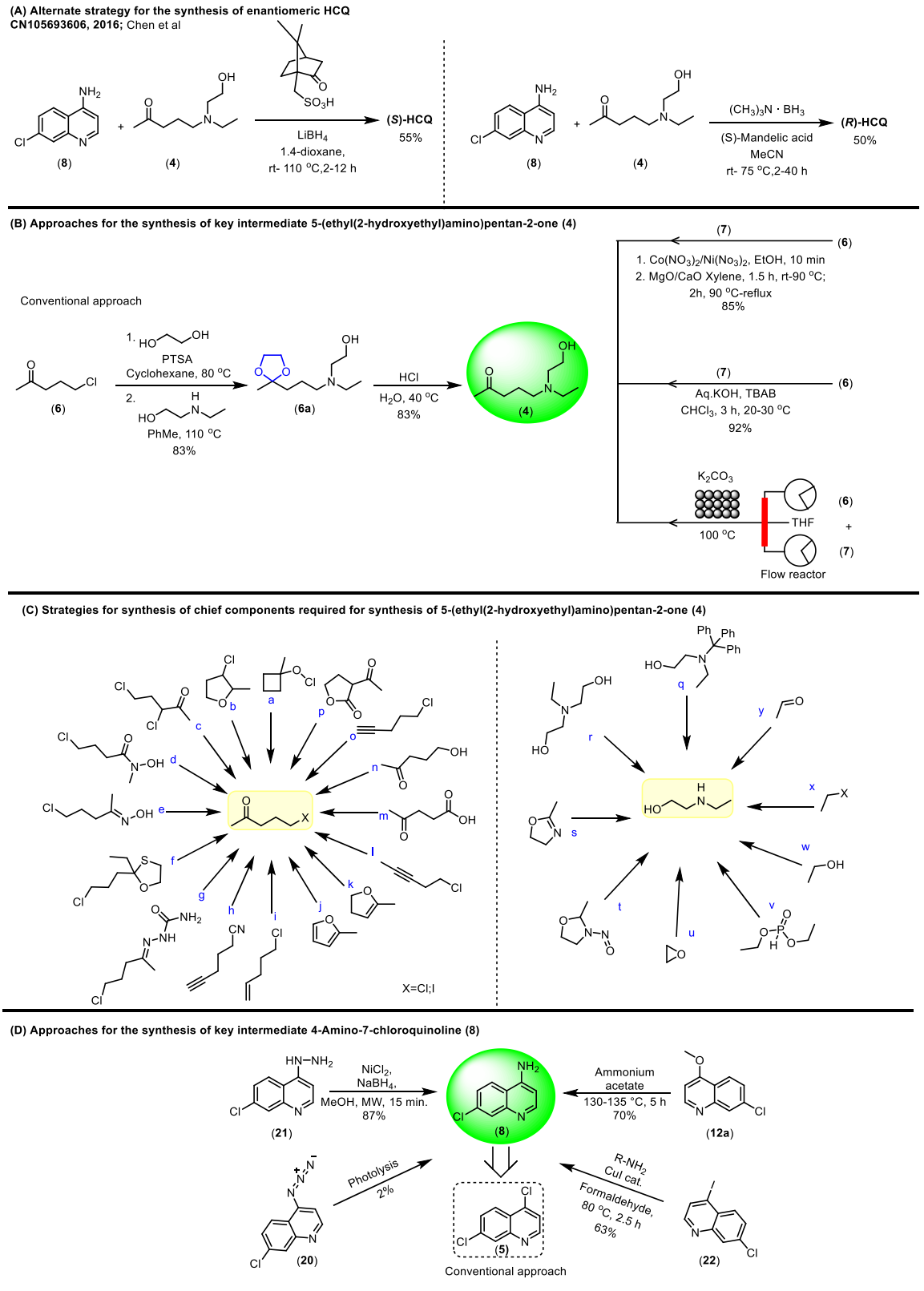
overcome the drawbacks of previous protocol by excluding the bases and utilizes protection-deprotection strategy to minimize the formation of desmethylated HCQ as a side product. Later on, Min *et al*.[79] introduce the synthesis of HCQ using the high-pressure technique at comparably lower temperature with low reaction time. Using a similar approach, Yu *et al*.[80] reported a sustainable and high-yielding continuous-flow synthesis of HCQ. (**Scheme 2A**.) Irrespective of reaction conditions utilised for the first synthetic strategy, the availability of key intermediate **2** is critical to meet the global demand.[81] The general approach for the synthesis of **2** involves the direct reductive amination of 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (**4**) in presence of ammonia[82] or reduction of corresponding oxime (**3**) [80] in a two-step procedure (Scheme 2B).

The other key intermediate, 4,7-dichloroquinoline (**5**) is relatively cheaper, commercially available and having the ease to synthesis using varieties of starting materials. The most convenient synthetic approach for **5** involves the use of 7-chloroquinolin-4(1*H*)-one (**12**) which in turn can be obtained by the reaction of 3-chloroaniline (**11**) with either ethoxy methylene malonic ester[83] (**13**) or diethyl ester of oxaloacetic acid[84] (**14**) following thermal heterocyclization and ester hydrolysis to yield **12a** followed by decarboxylation (Scheme 2C). In similar manner, reaction of methyl acrylate (**15**) in presence of stoichiometric tosyl chloride (**16**) with 2-amino-4-chlorobenzoic acid[85] (**11a**) or reaction of ethyl 3-oxopropanoate[86] (**17**) with **11** gives **12**. Alternatively, **12** can be prepared from reaction of **11** with Meldrum's acid (**18**)[87] via demethoxylation of **12b**.[88] In another approach, the synthesis of **5** is reported from 7-chloroquinolin-4(1*H*)-one (**12**) using chlorinated trichloroisocyanuric acid salt in the presence of $BMIMPF_6$ ionic liquid.[89] In alternate strategy (Scheme 1; strategy 2), Chen *et al*.[90] described the synthesis of enantiomeric **1** using 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (**4**) and 7-chloroquinolin-4-amine (**8**) to give (*R*)-HCQ and (*S*)-HCQ under reductive amination conditions following chiral resolution using 10-CSA and mandelic acid respectively (Scheme 3A). As discussed before, 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (**4**), a key intermediate for the synthesis of 2-((4-aminopentyl)(ethyl)amino)ethan-1-ol (**2**), is one of the major costs contributing factor for the overall synthesis of HCQ. Thus, its production is always looked upon for the economical large-scale up processes. With the current ongoing demand, availability of this key intermediate (**4**) and associated raw materials is critical for the bulk scale production to fulfill the global supply. The industrial route for the synthesis of **4** involves the protection-deprotection strategy using 5-chloropentan-2-one (**6**) as a starting material followed by S_N2 substitution with 2-(ethylamino)ethan-1-ol (**7**). Alternatively, Haijun and co-workers[91] utilized multifaceted transition-metal-catalysis for direct S_N2 reaction to give **4**. Although this protocol abolished the additional protection-deprotection step, the yield was sub-optimal coupled with use of toxic xylene as a reaction medium. In this context, Tie *et al.*[92] reported the green synthesis of **4** using TBAB (phase transfer catalyst) in Aq. alkaline

(water) : chloroform medium with 92% yield. Recently, Yu *et al.*[80] incorporated the use of high-yielding flow reactor for synthesis of **4** by passing THF dissolved mixture of **6** and **7** through preheated (100 °C) K_2CO_3 bead bed (Scheme 3B).



Scheme 2. A: Reported protocol for HCQ using synthetic strategy 1, B: Approaches for the synthesis of 2-((4-aminopentyl)(ethyl)amino)ethan-1-ol (**2**), C: Approaches for the synthesis of 4,7-dichloroquinoline (**5**).



Scheme 3. A: Alternate strategy for the synthesis of enantiomeric HCQ by Chen *et al.*, B: Approaches for the synthesis of key intermediate 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (**4**) based on the available literature, C: Available strategies for synthesis of chief component required for 5-(ethyl(2-hydroxyethyl)amino)pentan-2-one (**4**) synthesis, D: Approaches for the synthesis of key intermediate 4-Amino-7-chloroquinoline (**8**).

Irrespective the route of synthesis, the chief chemical required for synthesis of key intermediate **4** are haloketone, 5-chloropentan-2-one (**6**) and 2-(ethylamino)ethanol (**7**) (commercially available). The commonly reported methods for their synthesis utilizes cheap raw materials are summarized below in the **Scheme 3C** (a.[93]; b.[94]; c.[95]; d.[96]; e.[97]; f.[98]; g.[99]; h.[100]; i.[101]; j.[102]; k.[99,103]; l.[104]; m.[105]; n.[106]; n.[107]; n.[108]; o.[109]; o.[110]; p.[111,112,113]; q.[114]; r.[115]; s.[116]; s.[117]; t.[117]; u.[118]; v.[119]; w.[120]; x.[121]; x.[122]; y.[123]).

The other key intermediate 4-amino-7-chloroquinoline (**8**) can be obtained via amination of 4,7-dichloroquinoline (**5**) using ammonium carbonate[124] or liquid ammonia[125] or ammonia gas.[126] Although the yields are promising, the use of phenol as reaction medium requires careful handling especially on large scale production having high temperature. Additionally, in most of the cases, the hydrochloride salt of **8** was obtained as side product which further requires basic treatment, adding higher cost to the production. In a preliminary study Hollywoood *et al.*[127] reported the use of qunolylazides (**20**) as an alternative where its photo irradiation causes the formation of **8** while synthesizing various bicyclic azepine derivatives. Ganapathi *et al.*[128] reported the synthesis of **8** from 4-methoxy-7-chloroquinoline (**12b**) via demethoxylation using ammonium acetate as amine source with 70% yield. Gemma *et al*.[129] reported the synthesis of **8** using 7-chloro-4-hydrazinylquinoline (**21**) under microwave irradiation using $NaBH_4$ under nickel catalysis with 87% yield. Aillerie *et al.*[130, [131]] performed the copper catalysed cross-coupling reaction of 7-chloro-4-iodoquinoline (**22**) with ammonia (generated *in situ* from formamide) and ethanolamine for the synthesis of **8** (Scheme 3D).

6. Summary and Outlook

With the ongoing global surge in COVID-19 cases, limited information about 2019-nCoV, and lack of a definitive cure, the drug repurposing approach looks like the most promising tool to combat COVID-19. Under such circumstances, until recently, HCQ has turned out as valuable yet controversial therapeutics for its punitive role against COVID-19. As a result, a sumptuous amount of effort has been put forward to validates its therapeutic role for treating COVID-19 by extensive pre-clinical/clinical trials. On 17 June 2020, WHO announced the stoppage of HCQ Solidarity trial to find an effective COVID-19 treatment. However, the decision to stop HCQ's use in the Solidarity trial does not apply to the use or evaluation of hydroxychloroquine in pre- or post-exposure prophylaxis in patients exposed to COVID-19. Whatever it takes, the HCQ remains the WHO Model Essential Medicine and its accessibility to the people around the globe is an on-going demand. This in-turn demands cost-effective, safer, and environment-friendly large-scale synthesis of HCQ. In this context, inducing variability in raw materials via cheap and eco-green approach is the utmost essential to building a sustainable production particularly for small and medium scale enterprises (SMEs).

Funding Sources

Department of Pharmaceuticals, Ministry of Chemical and Fertilizers, Gov. of India
DST-SERB Ramanujan Fellowship (File No. SB/S2/RJN135/2017), Gov. of India
DST-SERB Start-up Research Grant (File No. SRG/2020/000658/CS), Gov. of India

Acknowledgment

The authors thank the Department of Pharmaceuticals (DoP), Ministry of Chemical and Fertilizers, and NIPER-Ahmedabad for financial support. DK hearty acknowledges Prof. Kiran Kalia, Director NIPER-A for her constant support, encouragement, and motivation. DK gratefully acknowledges the DST-SERB for the award of Ramanujan Fellowship (File No. SB/S2/RJN-135/2017) and Start-up Research Grant (File No. SRG/2020/000658/CS).

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