Molecular Modeling and Preliminary Clinical Data Suggesting Antiviral Activity for Chlorpheniramine (Chlorphenamine) Against COVID-19

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Abstract

Chlorpheniramine maleate, a widely used over-the-counter antihistamine, has been identified as a structural analog of aminoquinolines known to possess antiviral activity against the Betacoronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19). Structural similarities include the chlorophenyl group, pyridine ring, alkyl sidechain, and terminal tertiary amine; the comparison of aqueous energy-minimized structures indicates significant three-dimensional similarity as well. Preliminary clinical evidence supports these conclusions. The present study suggests that chlorpheniramine possesses antiviral activity against COVID-19.

Introduction

The coronavirus pandemic of 2019-2022 has caused over 5,300,000 deaths in over 272,000,000 confirmed cases by late 2021; the United States of America has been the most direly affected of all countries in the world, suffering nearly 15% of all fatalities [1]. The etiologic agent is the Betacoronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19), first identified in late 2019 in Wuhan, China [1]. Because the world population is naïve to this novel virus, extraordinary mortality has been experienced, and the need for effective therapeutics remains urgent.

Two related Betacoronaviruses have caused widespread mortality and morbidity in the recent past. The SARS-CoV-1 (“SARS”) outbreak of 2002-2004 began in the Guangdong province of southern China [2-5] and has been traced through Asian palm civets to cave-dwelling horseshoe bats [6]. The SARS virus caused a “severe acute respiratory syndrome” in 8,422 victims with a case mortality rate of 9.7% [5]. The Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak of 2012 began in the Arabian Peninsula and has been traced through dromedaries to bats [7,8]. MERS-CoV has infected 2,578 persons to date with a case mortality rate of 34.4% [8]. SARS-CoV-1 has not been detected since 2004 [9], whereas MERS-CoV reached a peak in 2015 and has diminished since then [8]. The SARS-CoV-2 pandemic has continued for three years to date; cases plateaued during early 2020 but have increased and oscillated since then [1], notably due to a surge of variant forms of SARS-CoV-2 such as delta, lambda, mu, and omicron [10]. Based on experience with SARS-CoV-1 and MERS-CoV, no accurate prediction of the SARS-CoV-2 pandemic duration is presently possible.

Currently, 25 COVID-19 vaccines have received emergency-use authorizations worldwide [11,12]; these vary in strategy and are RNA-liposomal, adenovirus-vector based, inactivated-virus, or protein-subunit vaccines. Vaccine efficacy is high, ranging from 67 to 95% [13]. Immunization is and will continue to be a very important means to control the SARS-CoV-2 pandemic, but some fraction of the population will not be protected, some individuals may not have access to the vaccine, contraindications may prevent some from being vaccinated, and vaccines prepared to earlier strains of the virus may have diminished efficacy presently. Accordingly, antiviral therapeutics are still required.

A wide variety of approaches have been taken toward the development of therapeutics for SARS-CoV-2 infections. Small-molecule drugs identified include remdesivir, favipiravir, ribavirin, oseltamivir (Tamiflu®), lopinavir, camostat, umifenovir (Arabidiol®), chloroquine, hydroxychloroquine, azithromycin, ivermectin, and glucocorticoids [14-19]. Interferons and immunoglobulins have also been explored [15,17].

Computational approaches have also contributed to our understanding of potentially active compounds that may be used to treat SARS-CoV-2 infections [20]. Specific approaches have included database searches, molecular modeling, and dynamics; targets have included, for example, the SARS-CoV-2 spike glycoprotein (S-protein) and main protease (Mpro, 3CLpro Nsp5) [18,21,22].
Chloroquine and hydroxychloroquine are antimalarials that also have been shown to interfere with the entrance of SARS-CoV-2 into human cells via the acetyl cholinesterase-2 (ACE2) receptor [15,16]. Clinical use of these drugs repurposed against SARS-CoV-2 has been controversial, but 80% of conclusive trials with significant study size were positive, and essentially 100% of early-stage disease studies were favorable. Negative trials were conducted on hospitalized patients with severe SARS-CoV-2 disease [23-26]. Nonetheless, 68% of late-stage studies have also shown efficacy. Thus, it appears that these aminoquinolines are best used with early to mid-stage disease. Adverse effects of hydroxychloroquine have been found recently, and these include lipidosis and podocytopathy [27], but these side effects must be weighed against therapeutic benefit.

Chlorpheniramine maleate (Chlorphenamine, 1-(2-pyridyl)-1-(4-chlorophenyl)-3-dimethylamino propane, SMILES: NC(C)CCC(C1=CC-C(C=C1)Cl)C2=CC=CC=N2) is an over-the-counter (OTC) antihistamine that was first prepared in 1951 [28] and has been in use for over 70 years. It has been found to be safe and effective with minimal side effects such as drowsiness and dry mouth, nose, and throat. Furthermore, it is widely available and is cost-effective. Chlorpheniramine also has been shown to be active as an antiviral against the human Ebola virus [29] and human influenza viruses [30]. The present work explores the activity of chlorpheniramine against SARS-CoV-2 by means of DrugBank structural searches, molecular modeling, and preliminary clinical evidence from a retrospective study.

**Materials And Methods**

**Molecular modeling studies**

The present approach to finding new candidate drugs for SARS-CoV-2 infections is somewhat different from others who have used screening or modeling. Rather, drugs of known activity, namely chloroquine and hydroxychloroquine that are broadly active against SARS-CoV-1, MERS-CoV, and SARS-CoV-2 and prevent the entry of the virus into cells, were employed in this study [15,51]. This approach seemed most fruitful as drugs that prevent cellular damage by the virus should be the most effective; few cells would be harmed, and the virus would remain in the bloodstream, respiratory system, or gastrointestinal tract to be detected and neutralized by the immune system or eliminated directly. Furthermore, a drug active against SARS-CoV-2 and readily available OTC was sought for this study.

A three-tiered approach was used in which the chemical structures of chloroquine and hydroxychloroquine were searched in the DrugBank database [32] against 13,580 drugs for related structures with Similarity Threshold = 0.35, molecular weight > 200, and Drug Types = Approved, Veterinary Approved, and Nutraceuticals; structural matches were re-screened against oral OTC drugs [33]; and the ultimately identified drugs were energy minimized with Spartan 10 software [34] (Hartree Fock 6-31-G* basis set in the presence of water with convergence). Energy-minimized structures were compared three-dimensionally to chloroquine, hydroxychloroquine, and chlorpheniramine crystal structures to achieve placement of related functional groups in similar portions of space. The present DrugBank search strategy was unique among others that have been reported and is based on drugs of known efficacy against SARS-CoV-2; the search threshold was set to 0.35 to survey related structures broadly. Energy minimization by this strategy should result in accurate structures equivalent to the conformation of the drugs in an aqueous solution. Software used in modeling also included Avogadro v1.2.0 [35], PubChem 3D Viewer v2.0 [36], LigandScout v4.45 [57], and Mercury v4.0 [58].

**Preliminary clinical data collection**

A retrospective human clinical study with chlorpheniramine maleate was performed online and participation in this study was entirely voluntary (https://www.surveymonkey.com/r/Q7RCCCV). Participants were recruited by word of mouth during the period of January 10, 2021, to November 16, 2021, and a majority of responses were received between January and February 2021. Fifteen questions were asked to the volunteers in this online questionnaire:

1. Demographic information.
2. Please say how you took chlorpheniramine (choose one option that best describes your situation).
3. What dose of chlorpheniramine did you take? (please select only one), 4. Date of known exposure to the COVID-19 coronavirus? (please leave blank if unknown), 5. Date of your COVID-19 viral antigen test (PCR or other; please leave blank if not tested), 6. Supplements, vitamins, and prescriptions you take, 7. Results of your COVID-19 test? (please leave blank if inapplicable), 8. When did you become ill with COVID-19? and begin to experience symptoms? (please leave blank if inapplicable), 9. How many days were you ill with COVID-19? 10. How ill did you become after you contracted COVID-19? 11. Were you hospitalized? 12. Your comorbidities or conditions (please check all applicable chronic conditions), 13. How many days were you ill with COVID-19? 14. How much do you believe that chlorpheniramine helped during your COVID-19 disease? and 15. Please provide any other information or feedback that you feel would be helpful to this retrospective study.

Lists of responses also included a free-response option, and sliders were provided, when appropriate, to ease response time. Volunteers provided information that covered November 2, 2020, to November 16, 2021, and many provided information anecdotally on persons who had also taken chlorpheniramine and remained healthy but did not complete the survey. Analysis of results was accomplished through online tools provided...
by the survey company and with Microsoft Excel. The confidentiality of all respondents and their information was protected.

**Results**

The results of a DrugBank structural search with chloroquine are shown in Table 1. Seventy-two drugs of a similar structure were found, with hydroxychloroquine as the highest score (0.950) and chlorpheniramine as a mid-score (0.377) drug. Fourteen classes of drugs are represented in the matches, including 19 antibiotics, 17 antineoplastic, nine neuroactive drugs, six anesthetics, five antimalarials, three antihistamines, two antifungals, two antiseptics, two anti-inflammatories, two non-steroidal anti-inflammatory drugs (NSAIDs), one anti-asthmatic, one antiemetic, one antiemetic, one antihistamine, and one cardiovascular drug.

| DrugBank Database Structural Match (class) | Score | DrugBank Database Structural Match (class) | Score |
|--------------------------------------------|-------|--------------------------------------------|-------|
| Hydroxychloroquine (AM)                    | 0.950 | Chlorpheniramine (AH)                      | 0.377 |
| Amodiaquine (AM)                           | 0.565 | Montelukast (AA)                           | 0.376 |
| Primaquine (AM)                             | 0.519 | Orbifloxacin (AB)                          | 0.376 |
| Dequalinium (AS)                            | 0.483 | Tofacitinib (AR)                           | 0.376 |
| Chlorquinaldol (AS)                         | 0.473 | Brimonidene (AI)                           | 0.372 |
| Proftavine (AB)                             | 0.466 | Erlotinib (AC)                              | 0.371 |
| Cabozantinib (AC)                           | 0.438 | Thenalidene (AH)                           | 0.369 |
| Dacomitinib (AC)                            | 0.429 | Sarafloxacin (AB)                          | 0.368 |
| Chloroxine (AB)                             | 0.428 | Difloxacin (AB)                            | 0.368 |
| Danofloxacin (AB)                           | 0.419 | Pefloxacin (AB)                            | 0.367 |
| Cariprazine (N)                             | 0.419 | Norfloxacin (AB)                           | 0.367 |
| Besifloxacin (AB)                           | 0.414 | Mepivacaine (AE)                           | 0.365 |
| Gefitinib (AC)                              | 0.411 | Degarelax (AC)                             | 0.363 |
| Tafenoquine (AM)                            | 0.409 | Ropivacaine (AE)                           | 0.363 |
| Clioquinol (AF)                             | 0.401 | Bupivacaine (AE)                           | 0.363 |
| Lenvatinib (AC)                             | 0.399 | Levobupivacaine (AE)                       | 0.363 |
| NCNPP                                       | 0.397 | Pergolide (N)                              | 0.362 |
| Domperidone (AV)                            | 0.396 | Mefloquine (AM)                            | 0.362 |
| Antrafenine (NS)                            | 0.394 | Boscalid (AF)                               | 0.362 |
| Sertindole (N)                              | 0.391 | Clomipramine (N)                           | 0.361 |
| Bosutinib (AC)                              | 0.389 | Floctafenine (AI)                          | 0.360 |
| Lomefloxacin (AB)                           | 0.389 | Vandetanib (AC)                            | 0.359 |
| Clofazimine (AB)                            | 0.387 | Tropisetron (N)                            | 0.359 |
| Sparfloxacin (AB)                           | 0.387 | Glasdegib (AC)                             | 0.358 |
| Grepaflaxacin (AB)                          | 0.385 | Perciozine (AE)                            | 0.356 |
| Neratinib (AC)                              | 0.385 | Clobazam (N)                               | 0.355 |
| Amsacrine (AC)                              | 0.383 | Bazedoxifene (AC)                          | 0.355 |
| Quinupramine (N)                            | 0.382 | Finafloxacin (AB)                          | 0.355 |
| Pradofloxacin (AB)                          | 0.380 | Bendamustine (AC)                          | 0.354 |
| Afatinib (AC)                                | 0.379 | Etdocaine (AE)                             | 0.354 |
| Ciprofloxacin (AB)                          | 0.379 | Trazodone (N)                              | 0.354 |
| DrugBank Database Structural Match (class) | Score | DrugBank Database Structural Match (class) | Score |
|-------------------------------------------|-------|-------------------------------------------|-------|
| Chloroquine (AM)                          | 0.950 | Pefloxacin (AB)                            | 0.381 |
| Amodiaquine (AM)                          | 0.564 | Norfloxacin (AB)                           | 0.381 |
| Primaquine (AM)                           | 0.529 | Bazedoxifene (AC)                          | 0.381 |
| Chloroquinaidol (AS)                      | 0.493 | Indoramin (CV)                             | 0.381 |
| Dequalinium (AS)                          | 0.474 | Erlotinib (AC)                             | 0.380 |
| Proflavine (AB)                           | 0.443 | Fentanyl (N)                               | 0.380 |
| Chloroxine (AB)                           | 0.440 | Boscalid (AF)                              | 0.379 |
| Gefitinib (AC)                            | 0.439 | Remifentanil (AE)                          | 0.378 |
| Dacomitinib (AC)                          | 0.436 | Dipyriramole (AT)                          | 0.378 |
| Danofloxacin (AB)                         | 0.433 | Tofacitinib (AR)                           | 0.378 |
| Besifloxacin (AB)                         | 0.426 | Sufentanil (AE)                            | 0.378 |
| Antrafenine (NS)                          | 0.423 | Alectinib (AC)                             | 0.377 |
| Bosutinib (AC)                            | 0.415 | Mepivacaine (AE)                           | 0.376 |
| Cariprazine (N)                           | 0.413 | Finafloxacin (AB)                          | 0.376 |
| Lenvatinib (AC)                           | 0.407 | Ropivacaine (AE)                           | 0.374 |
| Clioquinol (AF)                           | 0.404 | Bupivacaine (AE)                           | 0.374 |
| Lomefloxacin (AB)                         | 0.403 | Levobupivacaine (AE)                       | 0.374 |
| Sparfloxacin (AB)                         | 0.400 | Imiquimod (AC)                             | 0.374 |
| Grepafloxacin (AB)                        | 0.398 | Carprofen (NS)                             | 0.373 |
| Afatinib (AC)                             | 0.398 | Bendamustine (AC)                          | 0.372 |
| Domperidone (AV)                          | 0.398 | Chlorpheniramine (AH)                      | 0.371 |
| Montelukast (AA)                          | 0.396 | Perphenazine (N)                           | 0.371 |
| Orbifloxacin (AB)                         | 0.394 | Cetrorelix (H)                             | 0.370 |
| Ciprofloxacin (AB)                        | 0.393 | Diperodon (AE)                             | 0.370 |
| Enrofloxacin (AB)                         | 0.393 | Halofuginone (AS)                          | 0.370 |
| Sertindole (N)                            | 0.393 | Vandetanib (AC)                            | 0.368 |

A structural search with hydroxychloroquine, as shown in Table 2, found similar results with chloroquine scoring 0.950 and chlorpheniramine scoring 0.371. Drug classes remained the same.
These 72 drugs were screened against oral OTC medications, and only chlorpheniramine and deschlorpheniramine, both OTC antihistamines, remained. Deschlorpheniramine is the dextrorotatory isomer or R(+)-chlorpheniramine whereas chlorpheniramine maleate is prepared as a racemic mixture of $R$ and $S$ enantiomers. Thus, only one compound resulted from the OTC screening. The structure of chlorpheniramine is compared with chloroquine and hydroxychloroquine in Figure 1.
FIGURE 1: Comparison of Chlorpheniramine structure with those of Chloroquine and Hydroxychloroquine

Common structural features are indicated by colored ovals: chlorophenyl group (green), pyridine ring (orange), alkyl sidechain (black), and tertiary amine (purple). * = chiral carbons.

Chlorpheniramine shares four common structural features with chloroquine and hydroxychloroquine, namely chlorophenyl group, pyridine ring, tertiary amine, and alkyl sidechain. Structural differences include the presence of a secondary amine in chloroquine and hydroxychloroquine that chlorpheniramine lacks, fused chlorophenyl and pyridine rings (quinoline ring) in chloroquine and hydroxychloroquine, and longer alkyl sidechain and tertiary amine substituents in chloroquine and hydroxychloroquine.

Some properties of the screened drugs are compared in Table 3. Log(P) (octanol:water partition coefficient) values for the drugs shown in Table 3 are strongly positive which indicates significant hydrophobicity; in this respect, the log(P) of hydroxychloroquine is closer to that of chlorpheniramine than it is to that of chloroquine. Chlorpheniramine and deschlorpheniramine are considerably more water soluble than chloroquine and hydroxychloroquine. Lastly, the pKa of hydroxychloroquine lies midway between those of chloroquine and chlorpheniramine.
| Drug               | CAS Number | DrugBank code | MW (g/mol) | MW (maleate) | log(P)\text{ow} | H₂O Solubility (mg/L) | pKₐ  |
|-------------------|------------|---------------|------------|--------------|-----------------|-----------------------|------|
| Chloroquine       | 54-05-7    | DB00608       | 319.18     | -            | 4.63            | 0.14                  | 10.1 |
| Hydroxychloroquine| 118-42-3   | DB01611       | 335.18     | -            | 3.87            | 0.026                 | 9.67 |
| Chlorpheniramine  | 132-22-9   | DB01114       | 274.79     | 390.14       | 3.38            | 160                   | 9.13 |
| Dextropheniramine | 25523-97-1 | DB09555       | 274.79     | 390.14       | 3.39            | >100                  | 9.33 |

**TABLE 3: Properties of Final Drugs Under Study** *

* Data were obtained from PubChem.com, DrugBank.com, and the present work. The first molecular weight column is for the free base form of the drugs; the second is for the molecular weight of the maleate salt for the chlorpheniramine compounds. Log(P)\text{ow} refers to the octanol:water partition coefficient.

S-Chlorpheniramine, R-hydroxychloroquine, and R-chloroquine were chosen for further study as these enantiomers are known to be pharmacologically active [39,40]. The structures were energy minimized in the presence of water, and the final structures were aligned by the chlorophenyl ring, a common structural feature and a known hydrophobic pharmacophore of chloroquine, hydroxychloroquine, and chlorpheniramine [41]. Pharmacophores are molecular portions of the drug that confer biological activity when bound to a target macromolecule.

Comparison of the R-chloroquine energy-minimized structure to the crystal structure [42] in Figure 2a shows the alignment of the quinoline rings and secondary amines, but differing conformations for the alkyl sidechains with tertiary amines; the alkyl chain is slightly forward and right in energy-minimized chloroquine whereas it projects up, forward, and centered in the crystal structure. The same is true of hydroxychloroquine (Figure 2b), but the sidechain in the crystal structure [42] projects up, forward, and left compared to the energy-minimized structure which assumes a conformation like that of energy-minimized chloroquine (Figure 2a). Comparison of energy-minimized S-chlorpheniramine to the R-chlorpheniramine crystal structure [42,43] (Figure 2c) shows the overlap of the chlorophenyl groups and benzyl carbons, but the configuration of the alkyl chains and pyridine rings are, as expected, opposite one another; S-chlorpheniramine has the alkyl sidechain to the right compared to the R-isomer in which the sidechain projects backward. The pyridine ring of S-chlorpheniramine is behind the chlorophenyl ring with the nitrogen atom pointing up, whereas the pyridine ring in the R-isomer projects forward.
FIGURE 2: Aligned three-dimensional structures of Chloroquine, Hydroxychloroquine, and Chlorpheniramine

Energy-minimized structures of R-chloroquine, R-hydroxychloroquine, and S-chlorpheniramine are shown with silver bonds; crystal structures of S-chloroquine (CDQQUI), R-hydroxychloroquine sulfate (QOBHUL), and R-chlorpheniramine maleate (JEGWUN) are shown with black bonds. Color coding for atoms: carbon, black; nitrogen, blue; hydrogen, white; chlorine, green; oxygen, red; sulfur, yellow.

a. R-Chloroquine: energy minimized (front) aligned with the crystal structure.  
b. R-Hydroxychloroquine: energy minimized (front) aligned with the crystal structure.  
c. S-Chlorpheniramine: energy-minimized structure aligned with R-chlorpheniramine crystal structure (front).  
d. R-Chloroquine, R-hydroxychloroquine, and S-chlorpheniramine (front) aqueous energy-minimized structures aligned.

The energy-minimized structures are all similar, but the crystal structures vary in significant ways from each other as well as from the energy-minimized structures. The crystal structures were obtained from organic solvents (e.g. ethanol, ethyl acetate, DMSO) [44-46], whereas energy-minimization was performed in the presence of water. Thus, the energy-minimized structures appear to be more reliable representations of the aqueous behavior of chloroquine, hydroxychloroquine, and chlorpheniramine. The energy-minimized structures of these three drugs are aligned in Figure 2d. The chlorophenyl groups and equivalent "benzyl" carbons show a near-exact correspondence in all structures. Interestingly, the pyridine nitrogen of chlorpheniramine is very close in space to the secondary amines of chloroquine and hydroxychloroquine ("amine region"), and the alkyl sidechains and tertiary amines are clustered with nitrogen atoms in similar regions of space ("sidechain, tertiary amine"). This suggests that not only do these molecules have many structural elements in common, but they also share similar three-dimensional structural features.

For the present work, a retrospective clinical study was performed on 13 human participants who took chlorpheniramine (one to three 4 mg tablets per day) either preventively (78.6%) or post-exposure (21.4%). Out of the total participants, 54% had comorbidities (e.g. asthma, hypertension, Lyme disease, and blood-clotting disorders), 63% tested positive for the virus, and 38% became ill with COVID-19 disease (fatigue, sore throat, fever, chills, cough, shortness of breath, difficulty breathing, muscle ache, loss of taste and smell, and congestion). Preliminary results showed that no participant was hospitalized, and none died. Participants with COVID-19 disease recovered in an average of 7.8 ± 5.0 days, and respondents believed that chlorpheniramine had helped them an average of 65%.

Discussion

The strategy of searching for chemical structures related to those of chloroquine and hydroxychloroquine followed by screening results against oral, over-the-counter drugs yielded only chlorpheniramine. In other words, chlorpheniramine represents the only OTC drug that can be considered a possible therapeutic agent.
against SARS-CoV-2 to prevent its entry into human cells. This antihistamine has already been shown to possess antiviral action against the Ebola virus [29] and Influenza viruses [30] which supports its suggested use against the SARS-CoV-2 virus.

Energy minimization in the presence of water in conjunction with molecular modeling and alignment showed that all three drugs are similar three-dimensionally and, thus, may act equivalently against SARS-CoV-2 and other viruses. The three identified regions (chlorophenyl group, "amine region", and alkyl "sidechain, tertiary amine" region) may be important as possible pharmacophores. In studies with the Ebola virus, four hydrophobic interactions, which encompass the above three regions, were important pharmacophores of chloroquine [43].

Hydroxychloroquine appears to exhibit greater efficacy against SARS-CoV-2 than does chloroquine [15]. The results presented here show that chlorpheniramine shares properties with both aminooquinolines, but it more closely resembles hydroxychloroquine with which it shares similar log(P) and pKₐ values. This means that Chlorpheniramine and hydroxychloroquine are closely related by hydrophobicity and acid-base properties, both of which are known to be of significant importance in drug-receptor interactions. In addition, the three-dimensional structure of chlorpheniramine is more related to hydroxychloroquine than it is to chloroquine. Thus, with greater resemblance to the more active drug hydroxychloroquine, chlorpheniramine is more likely to have efficacy against SARS-CoV-2.

In silico molecular-dynamics calculations would be a useful complement to these results.

A recent clinical study from the University of Utah examined chlorpheniramine maleate nasal spray as a possible treatment for SARS-CoV-2 [47]; they found a 99.7% reduction of viral load after 25 min of treatment. This provides additional support for the conclusions of the present work. It is also in harmony with the preliminary retrospective clinical findings presented in this article. Clearly, prospective, double-blinded, placebo-controlled, randomized clinical studies with chlorpheniramine and dexchlorpheniramine will be important to establish firm pharmacologic links between the drug, the active enantiomer, and treatment of COVID-19 disease.

Conclusions

Present results from structural database searches, aqueous energy-minimized structure three-dimensional analyses, and preliminary clinical findings indicate that chlorpheniramine maleate, an inexpensive and widely available antihistamine, possesses antiviral activity against SARS-CoV-2.

Appendices

Appendix 1. Three-dimensional structure of R- chloroquine (R-Chloroquine aqueous.pdb) by energy minimization in the presence of water. This structure can be viewed by copying the text below and pasting it into a plain text file with the extension set as .pdb; the resulting file can be read with most 3D software.

HEADER
REMARK Spartan '10 exported M0001 R-Chloroquine aqueous.pdb
HETATM 1 C  UNK 0001 -4.865  -0.979  -0.247
HETATM 2 H  UNK 0001  -5.054   0.024  -2.112
HETATM 3 C  UNK 0001  -4.491  -0.087  -1.195
HETATM 4 C  UNK 0001  -3.055  -0.349   1.175
HETATM 5 C  UNK 0001  -3.351   0.730  -0.981
HETATM 6 C  UNK 0001  -4.144  -1.127   0.958
HETATM 7 C  UNK 0001  -2.626   0.610   0.218
HETATM 8 H  UNK 0001  -4.462  -1.851   1.682
HETATM 9 H  UNK 0001  -2.504  -0.476   2.088
HETATM 10 C UNK 0001  -1.975   2.349  -1.768
HETATM 11 H UNK 0001  -1.723   5.035  -2.557
HETATM 12 C UNK 0001  -1.187   2.331  -0.600
HETATM 13 H UNK 0001  -0.369   5.016  -0.498
HETATM 14 C UNK 0001  -1.490   1.633  -0.405
HETATM 15 N UNK 0001  -3.013   1.598  -1.969
HETATM 16 Cl UNK 0001  -6.268  -1.986  -0.504
HETATM 17 N UNK 0001  -0.717   1.439  -1.587
HETATM 18 C UNK 0001  -1.311   1.280  -2.377
HETATM 19 C UNK 0001   0.421   0.495  -1.643
HETATM 20 H UNK 0001   0.121  -0.471  1.235
HETATM 21 H UNK 0001  -0.069  -0.058   3.681
HETATM 22 C UNK 0001   0.785   0.305   3.112
HETATM 23 H UNK 0001   1.575  -0.426  -3.229
HETATM 24 H UNK 0001   1.110   1.239   3.553
HETATM 25 C UNK 0001   1.599  -1.015   0.816
HETATM 26 H UNK 0001   1.253  -1.226  -0.190
| HETATM | 27  | H   | UNK | 0001 | 1.927 | 1.962 | 1.237 |
|--------|-----|-----|-----|------|-------|-------|-------|
| HETATM | 28  | C   | UNK | 0001 | 2.780 | 0.045 | 0.722 |
| HETATM | 29  | H   | UNK | 0001 | 2.420 | -0.927 | 0.389 |
| HETATM | 30  | H   | UNK | 0001 | 3.234 | 1.520 | 0.150 |
| HETATM | 31  | H   | UNK | 0001 | 3.856 | 0.564 | -0.228 |
| HETATM | 32  | C   | UNK | 0001 | 3.415 | 0.762 | -1.209 |
| HETATM | 33  | H   | UNK | 0001 | 5.017 | -0.313 | -0.338 |
| HETATM | 34  | H   | UNK | 0001 | 3.676 | -1.552 | -1.375 |
| HETATM | 35  | H   | UNK | 0001 | 4.710 | -1.562 | -1.048 |
| HETATM | 36  | H   | UNK | 0001 | 5.296 | -1.624 | -1.960 |
| HETATM | 37  | C   | UNK | 0001 | 6.157 | 0.391 | -0.916 |
| HETATM | 38  | H   | UNK | 0001 | 5.984 | 0.627 | -1.970 |
| HETATM | 39  | H   | UNK | 0001 | 6.254 | 1.359 | -0.401 |
| HETATM | 40  | C   | UNK | 0001 | 7.478 | -0.355 | -0.777 |
| HETATM | 41  | H   | UNK | 0001 | 7.480 | -1.300 | -1.308 |
| HETATM | 42  | C   | UNK | 0001 | 5.985 | 0.627 | -0.916 |
| HETATM | 43  | H   | UNK | 0001 | 6.254 | 1.359 | -0.401 |
| HETATM | 44  | C   | UNK | 0001 | 7.478 | -0.355 | -0.777 |
| HETATM | 45  | H   | UNK | 0001 | 7.480 | -1.300 | -1.308 |
| HETATM | 46  | H   | UNK | 0001 | 5.985 | 0.627 | -0.916 |

CONECT 1  3  6  16
CONECT 2  3
CONECT 3  2  1  5
CONECT 4  6  7  9
CONECT 5  3  7  15
CONECT 6  1  4  8
CONECT 7  5  4  14
CONECT 8  6
CONECT 9  4
CONECT 10  12  11  15
CONECT 11  10
CONECT 12  10  14  13
CONECT 13  12
CONECT 14  7  12  17
CONECT 15  10  5
CONECT 16  1
CONECT 17  18  14  19
CONECT 18  17
CONECT 19  20  17  22  25
CONECT 20  19
CONECT 21  22
CONECT 22  21  23  24  19
CONECT 23  22
CONECT 24  22
CONECT 25  26  27  19  28
CONECT 26  25
CONECT 27  25
CONECT 28  29  30  25  32
CONECT 29  28
CONECT 30  28
CONECT 31  32
CONECT 32  31  33  28  34
CONECT 33  32
CONECT 34  32  36  38
CONECT 35  36
CONECT 36  35  37  34  46
CONECT 37  36
CONECT 38  39  40  34  41
CONECT 39  38
CONECT 40  38
CONECT 41  42  45  44  38
CONECT 42  41
CONECT 43  41
CONECT 44  41
CONECT 45  41
CONECT 46  45  47  48  36
CONECT 47  46
CONECT 48  46
Appendix 2. Three-dimensional structure of R-hydroxychloroquine (R-Hydroxychloroquine aqueous.pdb) by energy minimization in the presence of water. This structure can be viewed by copying the text below and pasting it into a plain text file with the extension set as .pdb; the resulting file can be read with most 3D software.

HEADER
REMARK Spartan '10 exported M0001 R-Hydroxychloroquine aqueous.pdb
HETATM    1  C   UNK  0001      -5.125  -0.826  -0.333
HETATM    2  H   UNK  0001      -5.264  0.356  -2.092
HETATM    3  C   UNK  0001      -4.725  0.144  -1.190
HETATM    4  C   UNK  0001      -3.297 -0.383   1.141
HETATM    5  C   UNK  0001      -3.565  0.907  -0.900
HETATM    6  C   UNK  0001      -4.407 -1.109   0.851
HETATM    7  C   UNK  0001      -2.844  0.655  0.281
HETATM    8  H   UNK  0001      -4.744 -1.892  1.502
HETATM    9  C   UNK  0001      -2.752 -0.615  2.036
HETATM   10  C   UNK  0001      -2.145  2.556 -1.531
HETATM   11  H   UNK  0001      -1.874  3.307 -2.251
HETATM   12  C   UNK  0001      -1.360  2.406 -0.371
HETATM   13  H   UNK  0001      -0.525  3.057 -0.205
HETATM   14  C   UNK  0001      -1.687  1.455 -0.548
HETATM   15  N   UNK  0001      -3.203  1.855 -1.800
HETATM   16  Cl   UNK  0001      -6.550 -1.768 -0.685
HETATM   17  N   UNK  0001      -0.921  1.302  1.724
HETATM   18  H   UNK  0001      -1.521  1.069  2.491
HETATM   19  C   UNK  0001      -0.208  0.346  1.691
HETATM   20  H   UNK  0001       0.099  0.011  3.136
CONECT   1  3  6  16
CONECT    2    3
CONECT    3    1    5
CONECT    4    6    9
CONECT    5    3    7    15
CONECT    6    1    4    8
CONECT    7    5    4    14
CONECT    8    6
CONECT    9    4
CONECT   10   12   11   15
Appendix 3. Three-dimensional structure of S-chlorpheniramine (S-Chlorpheniramine aqueous.pdb) by energy minimization in the presence of water. This structure can be viewed by copying the text below and pasting it into a plain text file with the extension set as .pdb; the resulting file can be read with most 3D software.

HEADER
REMARK Spartan ’10 exported M0001 S-Chlorpheniramine aqueous.pdb
HETATM  1  H  UNK  0001    1.169   -0.710   1.854
HETATM  2  C  UNK  0001    1.694   -0.262   1.032
HETATM  3  C  UNK  0001    3.083    0.857  -1.085
HETATM  4  C  UNK  0001    0.979    0.266  -0.041
HETATM  5  C  UNK  0001    3.076   -0.235   1.055
HETATM  6  C  UNK  0001    3.761    0.327  -0.008
HETATM  7  C  UNK  0001    1.697    0.822  -1.091
HETATM  8  H  UNK  0001    3.616   -0.645   1.887
HETATM  9  H  UNK  0001    1.175    1.239  -1.933
HETATM 10  H  UNK  0001    3.623    1.291  -1.906
HETATM 11 Cl  UNK  0001    5.511    0.365   0.018
HETATM 12 H  UNK  0001   -0.548    0.266  -0.079
HETATM 13 H  UNK  0001   -0.833    0.774  -0.990
HETATM 14 C  UNK  0001   -1.139    1.065   1.098
HETATM 15 H  UNK  0001   -0.925    0.551   2.027
HETATM 16 H  UNK  0001   -0.624    2.018   1.152
HETATM 17 H  UNK  0001   -5.142    0.517   1.091
HETATM 18 C  UNK  0001   -2.651    1.281   1.037
HETATM 19 H  UNK  0001   -2.947    1.827   1.938
Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other
relationships or activities that could appear to have influenced the submitted work.

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