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Design, Synthesis, and Development of 4-[(7-Chloroquinoline-4-yl)amino]phenol as a Potential SARS-CoV-2 Mpro Inhibitor

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A series of chloroquine analogs were designed to search for a less toxic chloroquine derivative as a potential SARS-CoV-2 Mpro inhibitor. Herein, an ANN-based QSAR model was built to predict the IC_{50} values of each analog using the experimental values of other 4-aminoquinolines as the training set. Subsequently, molecular docking was used to evaluate each analog's binding affinity to Mpro. The analog that showed the greatest affinity and lowest IC_{50} values was synthesized and characterized for its posterior incorporation into a polycaprolactone-based nanoparticulate system. After characterizing the loaded nanoparticles, an *in vitro* drug release assay was carried out, and the cytotoxicity of the analog and loaded nanoparticles was evaluated using murine fibroblast (L929) and human lung adenocarcinoma (A549) cell lines. Results show that the synthesized analog is much less toxic than chloroquine and that the nanoparticulate system allowed for the prolonged release of the analog without evidence of adverse effects on the cell lines used; therefore, suggesting that the analog could be a potential therapeutic option for COVID-19.

Introduction

Since its emergence in Wuhan, the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has taken more than 4.3 million lives around the world and as of today, more than 200 million active cases have been confirmed, with America and Europe being the most severely affected continents.[1] Officially declared a pandemic[2] in 2020, COVID-19 can present itself as an asymptomatic infection or as a mild, moderate or severe respiratory illness. Patients with underlying hereditary or acquired conditions are specially at risk of developing a severe disease.[3–5]

The virus spreads from person-to-person through respiratory droplets and aerosols.[5,6] Inside its host, the coronavirus spike (S) protein is recognized by angiotensin converting enzyme 2 receptors (ACE2),[7,8] which are highly expressed on the surface of lung epithelial cells,[9] and together with the serine protease TMPRSS2 allow the entry of the virus via endocytosis.[8] Once it enters the cells, the viral nucleocapsid is disassembled and the viral genetic material is released into the cytoplasm. There the viral RNA is replicated, transcribed, and translated[10,11] into viral polyproteins and proteases, which eventually become structural and nonstructural proteins that assemble with the genomic RNA of the virus to generate new virions that are released into the extracellular space and go on to infect neighboring cells.[11]

Even though ACE2 inhibition has been one of the main goals of COVID-19 prophylaxis,[12,13] the main protease or 3 C-like protease (Mpro or $3CL^{pro}$) is a potential therapeutic target as well as a target for drug development.[14,15] Mpro exclusively cleaves viral polyproteins to yield nonstructural proteins such as RNA and helicase-dependent RNA polymerases,[16] which are essential for the replication of the viral genome. Therefore, Mpro inhibition is a possible antiviral treatment strategy[14–17] for patients infected by SARS-CoV-2.

One of the most popular treatment strategies for COVID-19 has been drug repositioning, in which novel indications for currently marketed drugs are identified. This strategy is highly efficient and low-cost,[18] and it is strongly supported by computational approaches (*in silico*).[18–20] Among approved or still under study[21,22] drug repositioning, the repositioning of remdesivir,[23,24] lopinavir/ritonavir,[25–27] chloroquine and hydroxychloroquine[17,28–30] for mild to moderate coronavirus infections stand out.[20,31]

Drugs like chloroquine and hydroxychloroquine have been widely featured in clinical trials for the treatment of COVID-19.[32–36] Both are derivatives of 4-aminoquinoline, and have been described as immunosuppressant, anti-inflammatory, and antiviral drugs.[37–40] However, chloroquine has a narrow therapeutic index[40] which can cause cardiotoxicity because it prolongs the QT interval and inhibits sodium channels inducing ventricular arrhythmias, and cardiovascular collapse.[40,41] On the other hand, hydroxychloroquine is less toxic,[42] but still presents the same cardiovascular risks.[43–45]

Today, the early assessment of the efficacy, safety and toxicity of drug candidates can be carried out by low-cost and

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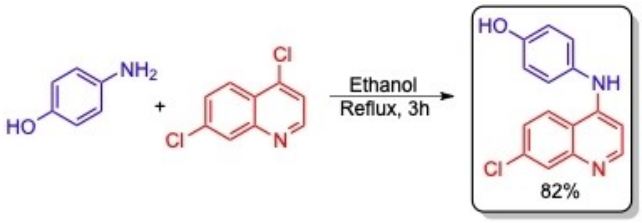
Table 1. Binding affinity (Kcal/mol), experimental IC_{50} and predicted IC_{50} of Mpro inhibitors.

Entry	Mpro Inhibitors	SBVS Average Energy (kcal/mol)	Experimental IC_{50} (nM)	LBVS Predicted IC_{50} (nM)
1	Chloroquine	−6.1	18.5[59]	27
2	Hydroxychloroquine	−6.6	21.5[59]	27
3	Quinine	−7.5	63.1[60,61]	38
4	Quinidine	−7.7	18[62]	38
5	Tafenoquine	−7.5	217[63]	65
6	Amodiaquine	−7.4	18.7[64]	29
7	Mefloquine	−7.7	24[65]	32
8	Quinacrine	−6.7	153[66]	56
9	Tetrandrine	−7.9	509[67]	354
10	Piperaquine	−7.5	32.2[60,61]	185
11	Pyronaridine	−8.9	5.8[59]	88
12	Hydroquinidine	−7.0	32[68]	38
13	Hydroquinine	−7.5	92[68]	38
14	4-((7-chloroquinolin-4-yl)amino)phenol	−7.8		12
15	4.((7-chloro-2-methoxybenzo[b][1,5]naphthyridin-10-yl)amino)phenol	−8.3		20
16	(S)-2-(6-sulfamoylnaphthalen-2-yl)propanoic acid	−7.0		15
17	(R)-2-(3-sulfophenyl)propanoic acid	−7.0		12
18	(S)-2-(6-(N-(but-1-en-2-yl)sulfamoyl)naphthalen-2-yl)propanoic acid	−7.0		22
19	3-(4′-((7′-methyl-2′-propyl-1H,3′H-[2,5′-bibenzo[d]imidazol]-3′-yl)methyl)-[1,1′-biphenyl]-2-yl)-1,2,4-oxadioazol-5(4H)-one	−9.3		116
20	3′-((22′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)methyl-7′-methyl)-2?-propyl-1H,3′H-2,5′-bibenzo[d]imidazole	−9.7		129
21	7′-methyl-3′-((2′-methyl-[1,1′bipheyl]-4-yl)methyl)-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole	−9.3		90

time-efficient[46,47] *in silico* methods like QSAR and molecular docking.[48–50] These methods can be productive strategies in public health emergency situations where time and resources are usually limited,[18,51] such as the COVID-19 pandemic.



Scheme 1. Synthesis of 4-((7-chloroquinolin-4-yl)amino)phenol.

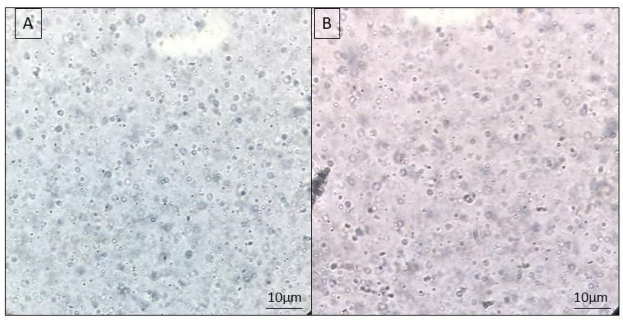


Figure 1. Light microscopy (400x). A) Unloaded NPs. B) Loaded NPs.

QSAR models identify the relationship between the physicochemical properties of chemical substances and their biological activities through statistical models built with machine learning algorithms such as multiple linear regressions (MLR), partial least squares (PLS) and artificial neural networks (ANN), which allow biological activities to be predicted for a new set of chemical structures.[49,52,53] Thus, these models are of special interest in drug discovery since they predict pharmacodynamic and pharmacokinetic parameters, like the IC_{50} and ADMET values[53,54] of new molecules built from the structural modification of the pharmacophore of a commercially marketed drug family.

Herein, to search for safer drug candidates for COVID-19, the *in silico* and *in vitro* studies of a novel chloroquine derivative designed through an ANN-based QSAR model are shown. Results demonstrate that the novel molecule can be considered a potential therapeutic option for the antiviral treatment of COVID-19.

Results and Discussion

The application of bioinformatic tools on medicinal chemistry has introduced robust methodologies which have helped drastically decrease chemical synthesis of random compounds.[46,47] Today, the two main strategies that aid drug discovery are ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS).[55] In this study both strategies were used to search for new potential SARS-CoV-2 Mpro inhibitors.

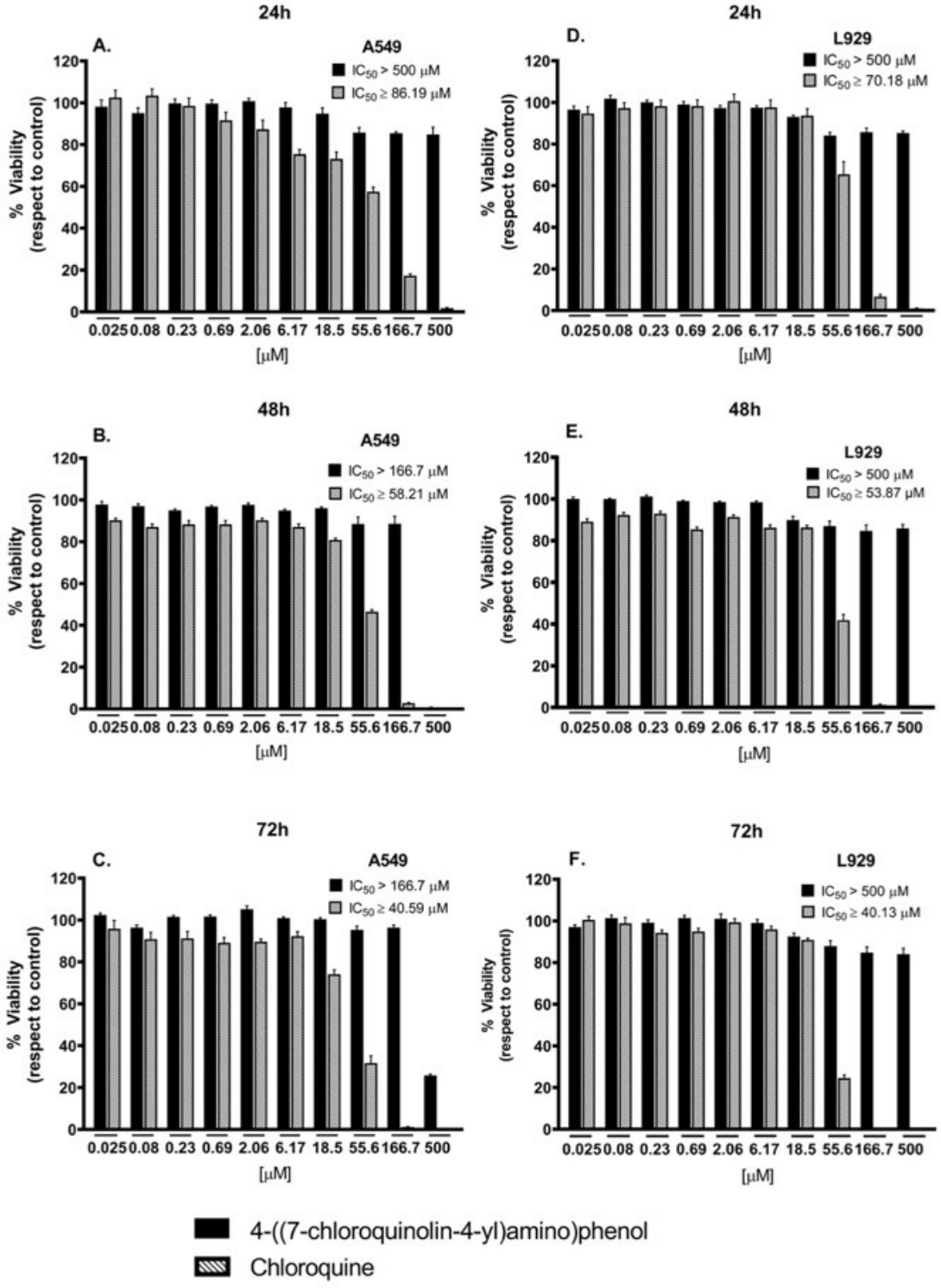


Figure 2. Effect of 4-((7-chloroquinolin-4-yl)amino)phenol and chloroquine on cell viability of A549 and L929 cells. Error bars represent standard error of the mean from three independent experiments in triplicates.

Structural analogs of chloroquine have proved effective against SARS-CoV-2 *in vitro*,[42,56,57] however, their effectiveness *in vivo* hasn't been demonstrated and their significant toxicity hasn't allowed their use as effective treatment options.[40,58] Therefore, we set out to study all commercially available chloroquine analogs with a defined therapeutic target and built an ANN that enabled the prediction of the IC_{50} values of a new set of chloroquine analogs with safer cytotoxic profiles and higher binding affinities to Mpro. For this purpose, as described in the methodology, an ANN with backpropagation was built

which allowed after a systematic analysis, the selection of three molecular descriptors (ATSC4p, ZMIC0, MLFER_A) via Pearson correlations. These descriptors, the reported experimental IC_{50} values of the training set and 1600 hidden nodes yielded a determination coefficient (R^2) of 0.899, which provided a tool with which to calculate the theoretical IC_{50} values of the training set (table 1, entries 1–13). Then, with the IC_{50} values (experimental and theoretical) of the commercially available chloroquine analogs, 8 new analogs were designed and their corresponding theoretical IC_{50} values were calculated (table 1, entries 14–21).

Afterwards, the binding affinity of all analogs to Mpro was determined by means of SBVS via molecular docking. As shown in table 1, entries 1–13 display the energy values in kcal/mol of the commercially available analogs while entries 14–21 show the energy values of the new analogs; it can be observed that although entries 19–21 presented the highest binding energies, their IC_{50} values were three times greater than that of chloroquine, which is enough to rule them out as potential candidates for Mpro inhibition. Nevertheless, entries 14 and 15 were considered the best candidates, although only entry 14 (4-((7-chloroquinolin-4-yl)amino)phenol) was chosen for synthesis because it had the lowest IC_{50} value of all the compounds from table 1.

A previously described synthesis[69] was used to obtain 4-((7-chloroquinolin-4-yl)amino)phenol hydrochloride, but for solubility and cytotoxicity assays 4-((7-chloroquinolin-4-yl)amino)phenol was obtained according to Scheme 1.

Once 4-((7-chloroquinolin-4-yl)amino)phenol was characterized, it was incorporated into the chosen vehicle. Particulate systems for drug delivery are an alternative to enhance the bioavailability and reduce the toxicity of active ingredients.[70] Due to their nanometric size and thus greater superficial area, nanoparticles can transport active compounds to the different microenvironments that make up the respiratory tract.[71] Hence, biodegradable polymers like polycaprolactone (PCL) are being used in the development of delivery systems for molecules with antiviral activity, especially against SARS-CoV-2,[72] due to their biodegradability and low toxicity.

The emulsion-solvent evaporation technique produced PCL nanoparticles with a size distribution of 250 nm $\pm$ 25 nm for the unloaded nanoparticles and 288 nm $\pm$ 35 nm for those loaded with the synthesized candidate (Figure 1). The resulting size distribution is ideal for the transport and release of active compounds across the upper and lower portions of the respiratory tract, which have been described as the infection sites of SARS-CoV-2.[71] On the other hand, the candidate's low solubility facilitated its incorporation into the oil phase of the o/w emulsion, resulting in entrapment efficiencies considered adequate for this methodology.[73] Moreover, the *in vitro* release assay showed that incorporation of the candidate into the oil phase allowed for a prolonged release of said candidate, which was maintained for days. Also, the obtained nanoparticles yielded a zeta potential of $+14.6 \pm 0.73$ mV, which promotes stability and favors adhesion to respiratory epithelial cells.[71]

Finally, the effect of the candidate and of the loaded and unloaded PCL nanoparticles on cell survival was evaluated using A549 and L929 cell lines, to determine their safety profiles. As shown in figure 2, the cytotoxic potential of 4-((7-chloroquinolin-4-yl)amino)phenol is considerably less than the one observed for chloroquine under the time and concentration intervals evaluated. Interestingly, chloroquine induced loss of viability on both cell lines at concentrations greater than 55.6 μM 48 and 72 h posttreatment, while cytotoxicity was observed at 166 and 500 μM 24 h posttreatment. Conversely, the candidate only induced loss of viability (less than 50%) on A549 cells at the maximum concentration evaluated (500 μM) 48 and 72 h posttreatment, whereas only a 25% loss was observed on L929 cells at 500 μM. In fact, the viability percentage was maintained above 80% under the rest of the concentrations and exposure times evaluated. On the other hand, as expected, both the loaded and unloaded PCL particles didn't show viability loss on either one of the cell lines used.

Conclusion

A series of potential SARS-CoV-2 Mpro inhibitors were rationally designed using an artificial neural network (ANN) with back-propagation to predict IC_{50} values. This ANN was built and trained using the reported IC_{50} values of several chloroquine and hydroxychloroquine analogs and yielded a determination coefficient (R^2) of 0.899. As a result, 4-((7-chloroquinolin-4-yl)amino)phenol, which presented an IC_{50} value of 12 nM and a binding affinity of -7.8 kcal/mol, was chosen for synthesis. After characterization, the synthesized compound was incorporated into PCL nanoparticles (288 nm $\pm$ 35 nm), and its cytotoxicity against that of chloroquine was evaluated using A549 and L929 cells, showing that 4-((7-chloroquinolin-4-yl)amino)phenol has a safer cytotoxic profile than chloroquine.

Supporting Information Summary

In the supplementary information is t the methodology for SBVS, LBVS, descriptor vs descriptor correlation, descriptor correlation vs $IC_{50,}$ experimental IC_{50} VS predicted IC_{50}, R^2 According to hidden layer nodes, characterization, NMR Spectra, preparation of nanoparticles, HPLC of 4 - ((7-chloroquinoline-4-yl) amino) phenol and in vitro cytotoxicity assay.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: ANN · Cytotoxicity · IC_{50} · Nanoparticles · Virtual Screening

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