Identification and validation of Triamcinolone and Gallopamil as treatments for early COVID-19 via an in silico repurposing pipeline

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Summary
SARS-CoV-2, the causative virus of COVID-19 continues to cause an ongoing global pandemic. Therapeutics are still needed to treat mild and severe COVID-19. Drug repurposing provides an opportunity to deploy drugs for COVID-19 more rapidly than developing novel therapeutics. Some existing drugs have shown promise for treating COVID-19 in clinical trials. This \textit{in silico} study uses structural similarity to clinical trial drugs to identify two drugs with potential applications to treat early COVID-19. We apply \textit{in silico} validation to suggest a possible mechanism of action for both. Triamcinolone is a corticosteroid structurally similar to Dexamethasone. Gallopamil is a calcium channel blocker structurally similar to Verapamil. We propose that both these drugs could be useful to treat early COVID-19 infection due to the proximity of their targets within a SARS-CoV-2-induced protein-protein interaction network to kinases active in early infection, and the APOA1 protein which is linked to the spread of COVID-19.

\textbf{Keywords}

COVID-19, Triamcinolone, Gallopamil, drug repurposing, artificial neural network, drug mechanism, virus replication

\textbf{Introduction}

The novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes Coronavirus disease 2019 (COVID-19), was first identified in Wuhan in December 2019 and by June 2021 had spread to 192 countries or regions and infected over 165 million people, killing more than 3 million people\footnote{1}. COVID-19 infection has a wide spectrum of symptoms. Those with mild infections may be asymptomatic, have anosmia\footnote{2} or mild respiratory symptoms\footnote{3}, whereas severe infections lead to acute respiratory distress syndrome (ARDS) and potentially death\footnote{4}.

Treatments are urgently needed to reduce the severity and mortality rate of COVID-19. However development of a novel therapeutic takes many years\footnote{5} and has high attrition rates, often due to safety and toxicity\footnote{6}. Drug repurposing is the repositioning of existing...
approved or investigational drugs to therapeutic uses beyond the scope of the original medical indication. This approach offers de-risked possibilities to identify safe, effective treatments faster and more economically than novel drug development.

Despite impressive progress in the past year, there is still a need for COVID-19 treatments. WHO recommends Dexamethasone for severe COVID-19 but also advises against its use in non-severe COVID-19 patients. In the US, the FDA approved Veklury (Remdesivir) for patients who are hospitalised with COVID-19. Although there are no approved treatments for mild COVID-19, emergency use authorisation has been granted for several monoclonal antibodies on mild-to-moderate patients, but only for those who are at risk of severe disease, and only approved via intravenous administration. Monoclonal antibodies are expensive with one dose of Bamlanivimab (which has emergency use authorisation) costing $1,250 per vial. Chemical structure similarity is based on the concept that structurally similar molecules often share similar biological function, and is a concept frequently used in drug discovery. Our in silico approach predicts potential candidates for repurposing to treat COVID-19 based on structural similarity to drugs already in clinical trials (CTDs) for COVID-19. CTDs were used as a starting point as there are few FDA-approved drugs for COVID-19. On the other hand, there are sufficient number of CTDs that are assumed to have some hypothesised utility in COVID-19, and at least one has been approved.

Treatments during the early stages of COVID-19 infection, which might also prevent the progression from mild to severe disease, would be particularly useful to relieve the burden on hospitals. We hypothesise that drugs which affect viral replication pathways could be used to treat early COVID-19, preventing hospitalisation.

Results

Identification of chemical structure similarity
To identify drugs which could be safely and rapidly deployed to treat COVID-19, we used the ChEMBL API to computationally predict structurally similar drugs (SSDs) to drugs in clinical trials for COVID-19 (C19-CTDs); this was based on the Tanimoto coefficient (Tc), a similarity measure widely used in molecular fingerprint comparison15. There were 7,682 compounds in clinical trials for any indication at Phase II or higher (including approved). Figure 1 outlines the workflow we used to identify which of these are similar to C19-CTDs, and the filtering steps to identify those with potential for treating early-stage COVID-19. Among these 7,682 compounds, 101 compounds were determined to have structural similarity to 185 C19-CTDs, with a Tanimoto coefficient > 70 (Figure 1). Figure 2A shows the number of SSDs, with the cut off shown by the dashed line. The top 10 SSDs by similarity score are shown in Figure 2. Drug structural similarity screening (A) Histogram showing the number of drugs in Phase II+ with a Tc > 40 similar to C19-CTDs. The cut off for similarity of 70 is shown by the blue dashed line. The red box highlights the drawn structures (B-L). Heatmap of the chemical structures of the top 10 SSDs by similarity showing their structural similarity to C19-CTDs from which they were predicted. The structural differences are highlighted in red. (B) Tafimoxifen predicts Afimoxifene. (C) Verapamil predicts Gallopamil. (D) Sirolimus predicts (E) Everolimus, (F) Ridaforolimus, (G) Temirolimus, and (H) Zotarolimus. (I) Dexamethasone predicts Triamcinilone. (J) Icosapent predicts Docosapentaenoic acid. (K) Amoxicillin predicts Ampicillin. (L) Mannitol predicts Xylitol.2A with a red box.2B-L (and highlighted in Figure 2. Drug structural similarity screening (A) Histogram showing the number of drugs in Phase II+ with a Tc > 40 similar to C19-CTDs. The cut off for similarity of 70 is shown by the blue dashed line. The red box highlights the drawn structures (B-L). Heatmap of the chemical structures of the top 10 SSDs by similarity showing their structural similarity to C19-CTDs from which they were predicted. The structural differences are highlighted in red. (B) Tafimoxifen predicts Afimoxifene. (C) Verapamil predicts Gallopamil. (D) Sirolimus predicts (E) Everolimus, (F) Ridaforolimus, (G) Temirolimus, and (H) Zotarolimus. (I) Dexamethasone predicts Triamcinilone. (J) Icosapent predicts Docosapentaenoic acid. (K) Amoxicillin predicts Ampicillin. (L) Mannitol predicts Xylitol.2A with a red box).
Prioritization of SSDs which have sufficient biological distinction from the C19-CTDs

To select the most promising SSDs for the treatment of early-stage COVID-19, we applied multiple stages of filtering (Figure 1). The rationale for our approach is to expand the array of drugs which are being investigated and used to treat COVID-19 during this pandemic. Although we selected SSDs due to structural similarity to C19-CTDs, we wanted to avoid focusing on drugs which are already being heavily studied for utility in treating COVID-19. For this reason, we retained only SSDs which do not have the same utility as the C19-CTD which they were predicted from. We removed SSDs that target the same proteins, or which we predicted to impact the same biological pathways as their corresponding C19-CTDs, retaining only those which will elicit different therapeutic effects.

In the first stage of filtering, the list of SSDs was cleaned to remove any drugs which were effectively duplicated (Figure 1). For instance, Taribavirin and Taribavirin hydrochloride were both identified as being similar to Ribavirin (similarity score 76.2). However, since Taribavirin hydrochloride is the acid salt of Taribavirin, and once solubilized in the body (at approximately pH 7.4), both structures will exist in the same deprotonated form and have the same behaviour, these were considered as effective duplicates and the acid salt was removed from the filtered list of SSDs. After the removal of effective duplicates, 78 SSDs remained.

Secondly, we excluded antineoplastic agents from our list of SSDs. Since these cancer drugs may cause severe adverse drug reactions in patients\textsuperscript{16–18}, we concluded that they would not be suitable to treat mild COVID-19 infections. We eliminated five antineoplastic agents, which have ATC code L01, due to this toxicity issue. This reduced the list to 73 SSDs.

Thirdly, we eliminated any SSD with exactly the same target proteins as its corresponding C19-CTD as we reasoned that it would be unlikely for the two drugs to have different therapeutic effects. After this step, there were 28 SSDs. Further filtering was done to ensure that retained SSDs were targeting enough different proteins (and sufficiently
separated on a COVID-19 protein-protein network) from their corresponding C19-CTD so as to be sufficiently biologically distinct.

We used the SARS-CoV-2-induced protein (SIP) network at 24 hours generated by Han et al.\textsuperscript{19} as the base network to investigate this in the context of COVID-19. This network contains the directly interacting proteins (DIP) of SARS-CoV-2 identified by mass spectrometry\textsuperscript{20}, differentially expressed proteins (DEP) after SARS-CoV-2 infection identified by mass spectrometry\textsuperscript{21}, and a layer of connections between the two built using known protein-protein interaction (PPI) data as described by Han et al.\textsuperscript{19}. We used the 24 hour SIP network because the key proteins are more enriched in viral replication and there are a significantly increased number of protein-protein interactions (PPI) in RNA- or viral-replication-related pathways\textsuperscript{19}, which we wanted to examine impact upon.

If the average distance between the targets of any SSD and its corresponding C19-CTD in the SIP 24-hour network\textsuperscript{19} was less than 1, the drug was filtered out (see Methods). Through this analysis, we identified 17 (21\%) SSDs predicted from 11 C19-CTDs.

**Mechanism of action analysis of SSDs in relation to COVID-19**

To establish the Mechanism of Action (MoA) of the 17 identified drugs, we characterised the pathways that are targeted by each drug. The purpose of the MoA analysis was first to discover SSDs which have different MoA to their corresponding C19-CTD and to better understand whether these identified SSDs would be useful in treating early-stage COVID-19.

An initial pathway enrichment test performed on the target proteins of all 28 drugs (17 SSDs and 11 C19-CTDs) which were found in the SIP 24-hour network identified a set of 488 biological pathways. As a measure of the accuracy of this enrichment, we then calculated the precision and recall of the enrichment test to produce an F1 score. The F1 scores were calculated for each drug-pathway association, and we generated an F1 score matrix for all 28 drugs, including an F1 score for 488 pathways.

The unsupervised training of a Self-Organizing Map (SOM) with the F1 score matrix generated 28 SOM component plane heatmaps (Supplementary Figure 1). Each heatmap
represents the pattern of associated pathways for a drug and each hexagon in the heatmap has unique pathways which have the same position across all heatmaps (corresponding to drugs). As each heatmap in the SOM results maintains the same position for each hexagon, this allows direct visual comparison between pathways affected by each drug. To exclude SSDs with a similar drug-pathway association as their C19-CTD, we calculated the correlation coefficient ($r$) between SOM heatmap values for each pair. We excluded SSDs which were correlated with their corresponding SSD ($r > 0.5$) to narrow our focus on SSDs which had different associated pathways than their corresponding C19-CTD.

This identified 12 SSDs that were similar to eight C19-CTDs (Figure 3A). The SSDs identified were Triamcinolone and Beclomethasone (which are similar to Dexamethasone), Omega-3-Carboxylic Acids (which is similar to Icosapent), Beta Carotene (which is similar to Isotretinoin), Dextrothyroxine (which is similar to Liothyronine), Xylitol (which is similar to Mannitol), Clinidipine (which is similar to Nimodipine), Gallopamil (which is similar to Verapamil) and four SSDs similar to Zinc Sulfate. These SSDs were filtered to ensure that they target different proteins and different pathways to their corresponding C19-CTDs.

**Identification of SSDs which have potential in treating early COVID-19**

To assess whether any of our predicted drugs would be useful in treating early COVID-19 infection before it develops into severe disease, we determined which SSDs impacted on pathways related to viral replication. Viruses replicate by hijacking the processes of the host cell; they cannot replicate by themselves. From the SOM analysis, the pathways associated with each SSD had been established (Supplementary Figure 2). The 488 pathways assigned to hexagons in the SOM heatmap were clustered using a unified distance matrix (U-matrix, Figure 3B) that captures the distribution of the trained artificial neurons in the data space (Figure 3C). The SOM also provided the clustering information based on the U-matrix and number of hits (pathways) per hexagon (neuron) (Figure 3D). In addition, we calculated the Davies–Bouldin index (DBI) that provides the optimal number of clusters in $k$-means clustering (Figure 3E). Finally, the 448 pathways were classified into 10 pathway clusters.
(Figure 3F, Supplementary Table 1). We used this information to identify which of the remaining SSDs were impacting on pathways involved with viral replication. These are also highlighted in Figure 3F. We reasoned that viral replication-related drugs may be more useful for the treatment of early-stage disease, while drugs whose targets are linked with immune-response-associated pathways may be better suited for later-stage COVID-19 infection.

As an example of this approach, we present the two SSDs which were structurally similar to Dexamethasone. The correlation coefficient between Dexamethasone and both SSDs (Beclomethasone and Triamcinolone) was lower than 0.5, so both were sufficiently different from Dexamethasone to be considered promising drug candidates for expanding the approach to COVID-19 treatments (Figure 3A1, Supplementary Table 2). From Beclomethasone’s SOM heatmap, Beclomethasone was found to be associated with the ESR, Glycosylation, MAPK, AP-1 and PLA2 pathways (Figure 3F), and these associated pathways are predominantly related to the immune response. Triamcinolone on the other hand was found to be associated with the high-density lipoprotein (HDL) remodelling pathway (Figure 3F), a process which is reported to be strongly related to coronavirus replication \(^{22,23}\), so we studied Triamcinolone further as a potential treatment for early-stage COVID-19 infection.

Using the same approach, we also identified Gallopamil, Omega-3-Carboxylic Acids and Beta Carotene for treating COVID-19 at an early stage of infection. The SOM heatmaps for Gallopamil and Triamcinolone are highly similar (Figure 3A1 and 3A7), and unsurprisingly Gallopamil is also associated with HDL remodelling (Figure 3F). Omega-3-Carboxylic Acids is associated with fatty acid beta-oxidation, which is related to virus replication\(^{24}\). Beta Carotene is associated with Retinoic acid (RA), which is also related to virus replication. However, Omega-3-Carboxylic Acids and Beta Carotene were discontinued\(^{25}\), so further analysis into the potential in early COVID-19 was conducted on Triamcinolone and Gallopamil only.
**Triamcinolone and Gallopamil targets impact SARS-CoV-2 replication**

To validate the activity of Triamcinolone and Gallopamil on viral replication of SARS-CoV-2, we performed *in silico* validation on their targets within SIP network at 24-hours after infection\(^{19}\). To establish if these drugs impact on processes occurring early in COVID-19 infection, we measured the proximity of the targets of each drug to a group of kinases that are active in the first 24-hour post infection with SARS-CoV-2. Bouhaddou *et al.*\(^{26}\) predicted the activity of these kinases based on the regulation of their known substrates. All these kinases were present in the SIP 24-hour network we used for validation. Both Triamcinolone and Gallopamil have 3 targets in the SIP 24-hour network, and for both drugs, their targets are closer on average in this network to the active kinases identified by Bouhaddou *et al.*\(^{26}\) than 10,000 randomly selected groups of three proteins (Figure 2. *In silico* validation of Gallopamil and Triamcinolone. (A) Histogram of average distances between 10,000 groups of 3 proteins and kinases active in SARS-CoV-2 infection. The distance of the Gallopamil and Triamcinolone targets are indicated with arrows, and the red dashed line shows the permutation cut-off for the 5% of protein groups closest to the kinases (p-value = 0.05) (B) Subnetwork of Gallopamil and Triamcinolone target proteins and their direct interactors which are important in COVID-19 infection. (C) Boxplots showing fold-change in moderate patients with covid-19 of a target protein of the drug and neighbour proteins of the target protein. The control results in the boxplot show fold-change of random genes with the same number of a target protein and the neighbour proteins of the target protein. Significance was tested by the Mann Whitney U test (p-value <0.05). A). Both drugs directly interact with some of these active kinases (as shown in Figure 2. *In silico* validation of Gallopamil and Triamcinolone. (A) Histogram of average distances between 10,000 groups of 3 proteins and kinases active in SARS-CoV-2 infection. The distance of the Gallopamil and Triamcinolone targets are indicated with arrows, and the red dashed line shows the permutation cut-off for the 5% of protein groups closest to the kinases (p-value = 0.05) (B) Subnetwork of Gallopamil and Triamcinolone target proteins and their direct interactors which are important in COVID-19 infection. (C) Boxplots showing fold-change in moderate patients with covid-19
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To check both drugs’ potential efficacy for inhibiting SARS-CoV-2 virus replication, we investigated the activity levels (expression patterns) of the target genes of the two drugs in the moderate COVID-19 group of patients because virus replication is known to be activated in moderate COVID-19 patients but decreased in severe patients27. First, we generated a list of the proteins and pathways that are targeted by the two drugs using the SOM results (Figure 1. Drug-pathway association study (A) 21 SOM component plane heatmaps. In each plane heatmap, the hexagon in a certain position corresponds to a set of unique pathways which has the same position across all heatmaps (drugs). Each hexagon is coloured according to the distance between corresponding data vectors of neighbour
neurons, with low distance areas (bright yellow) indicating high data density. Mapping of the 21 drugs to each neuron (pathway) based on matching rates and inspection of examples from each cluster (1-8). (B) Unified distance matrix (U-matrix) of SOM result. (C) Principal component (PC) projection of SOM represents the distribution of trained neurons in the data space. (D) Colour code of SOM grid shows the clustering information and the number of hits (pathways) in each hexagon (neuron) (E) Davies-Bouldin index (DBI) indicates that 10 is the optimal number of clusters. (F) 10 pathway clusters and their names. F, Supplementary Figure 2). We next examined the directly interacting proteins of the drug's target proteins; that is, the one neighbour proteins of the target proteins on the SIP 24-hour network was included. We found that the proteins in the HDL remodelling pathway were significantly upregulated compared with the control (Mann Whitney U test p-value <0.05, Figure 2. In silico validation of Gallopamil and Triamcinolone. (A) Histogram of average distances between 10,000 groups of 3 proteins and kinases active in SARS-COV-2 infection. The distance of the Gallopamil and Triamcinolone targets are indicated with arrows, and the red dashed line shows the permutation cut-off for the 5% of protein groups closest to the kinases (p-value = 0.05) (B) Subnetwork of Gallopamil and Triamcinolone target proteins and their direct interactors which are important in COVID-19 infection. (C) Boxplots showing fold-change in moderate patients with covid-19 of a target protein of the drug and neighbour proteins of the target protein. The control results in the boxplot show fold-change of random genes with the same number of a target protein and the neighbour proteins of the target protein. Significance was tested by the Mann Whitney U test (p-value <0.05). C, Supplementary Table 3). As a control, we randomly selected the same number of proteins as the target protein plus one neighbour proteins of the HDL-remodelling pathway. Of the targets of the two drugs, ACE and SERPINA6 directly interacted with APOA1 in the SIP 24-hour network. APOA1, which is a major transporter of HDL-cholesterol, has been linked to the spread of COVID-19 and is essential for HDL metabolism and remodelling, potentially explaining why the HDL remodelling pathway was upregulated. The subnetwork for each drug (Figure 2. In silico validation of Gallopamil and Triamcinolone. (A) Histogram of average
Discussion

In this study, we have taken an in silico approach to highlight two drugs that have structural similarity to drugs already in COVID-19 clinical trials but can be differentiated from these existing drugs. Importantly, these have a distinct mechanism of action related to virus replication, and we therefore propose they may be useful in treating early-stage COVID-19 patients.

Triamcinolone is a corticosteroid identified on the basis of its similarity to C19-CTD Dexamethasone, and is approved for the treatment of a range of inflammatory conditions including allergies, arthritis, asthma and skin problems. Results from the RECOVERY trial showed that Dexamethasone reduces death in COVID-19 patients by approximately one-third\(^\text{30}\). Triamcinolone inhibits nuclear factor kappa-B, which decreases the production of pro-inflammatory signals such as interleukin-6 (IL-6), interleukin-8, and monocyte chemoattractant protein-1\(^\text{31}\). IL-6 plays an important role in cytokine release syndrome\(^\text{32}\) which is triggered in severe COVID-19 patients. Sustained elevation of IL-6 is also linked to
death in acute respiratory distress syndrome\textsuperscript{33} (ARDS), the respiratory condition experienced by critical COVID-19 patients.

Here we propose utility for Triamcinolone treatment in early COVID-19 infection to prevent the early activity of the virus. This is based on the proximity of its targets to key COVID-19 proteins including direct interactions with: SARS-CoV-2 DIP and DEP proteins; APOA1, which has been linked to the spread of COVID-19\textsuperscript{28}; as well as kinases which are active in early SARS-CoV-2 infection (e.g. PIK3CA, AKT1 and 5 MAPK proteins). The PI3K-AKT and MAPK signalling pathways are among those reported to be altered following SARS-CoV-2 viral infection.\textsuperscript{34}

Gallopamil is an L-type calcium channel blocker and an analogue of Verapamil. A study using natural language processing suggested calcium channel blockers were associated with decreased mortality in hospitalised patients with COVID-19 infection\textsuperscript{35}. Gallopamil is not yet approved for the treatment of any disease, although it has been trialled orally (Phase II) for severe asthma with no significant difference in adverse effects between patients receiving Gallopamil or placebo\textsuperscript{36}. Gallopamil targets MME, which is a direct interactor of ACE2. Since ACE2 is a cellular entry point for SARS-CoV-2 into human cells\textsuperscript{37}, this could be a possible mechanism through which Gallopamil may target SARS-CoV-2 viral replication. Additionally, Gallopamil also targets ACE, which directly interacts with the HDL remodelling pathway proteins APOA1, APOE and ALB, as well as kinases that are active in infection (AKT1, MAPK3, and MAPK1). This suggests Gallopamil may target similar pathways to Triamcinolone during early COVID-19 infection.

Our \textit{in silico} approach is based on publicly available data from online databases such as STITCH\textsuperscript{38} and ChEMBL\textsuperscript{39}, and studies published in response to the pandemic\textsuperscript{19,20,26,27}. By combining this information, we have predicted two drugs that interact with key pathways and proteins involved in early COVID-19 infection, suggesting this is an effective approach to take in this pandemic. It is likely that further diseases of zoonotic origin will emerge in the future\textsuperscript{40}, and we must be prepared to respond rapidly to future pandemic threats. This kind of
in silico approach allows for a quick and cost-effective approach to repurposing drugs, which could be deployed in such a situation.

The focus of this study on drugs that are in clinical trials for COVID-19 was a logical starting point given the urgent nature of the continuing COVID-19 pandemic, but has some obvious limitations. Firstly, as the controversy surrounding Hydroxychloroquine highlights, a drug merely being in a COVID-19 clinical trial does not mean it is effective (with the exception of Dexamethasone, which has been approved). Also, there are likely to be many relevant drugs that have been missed in this study as they are not structurally similar to drugs that have already been in a clinical trial for COVID-19. Lastly, STITCH DB was used to obtain target information for comparing C19-CTDs to SSDs; while this is an important and useful resource, it does not account for missing information or off-target effects. Although in silico validation showed promising results for Triamcinolone and Gallopamil, follow-up studies in experimental models will be required to verify these effects and support their clinical potential.

Triamcinolone and Gallopamil have been identified by our in silico approach as drugs with potential for the treatment of early-stage COVID-19. Of the two, Triamcinolone is already approved for other indications, so could be deployed quickly. Gallopamil has passed Phase II trials and could be quickly prioritised into COVID-19 trials. We conclude that both would be good candidates for further investigation in in vitro and in vivo models as well as clinical trials.

Experimental procedures

Resource availability

Lead contact
Further information and requests for resources and materials should be directed to and will be fulfilled by the lead contact, Namshik Han (nh417@cam.ac.uk)

Data availability
This study used publicly available data from online databases and other research papers.
Code availability

Code used for this study is available at https://github.com/wchwang/COVID-19.HfH.

Obtaining list of structurally similar drugs

A list of COVID-19 clinical trial drugs (C19-CTDs) was obtained from DrugBank\textsuperscript{41}, an online bioinformatics and chemoinformatics database that contains data on drugs and their targets. The ChemMBL API for chemical structural similarity accepts input in the simplified molecular-input line-entry system (SMILES), an ascii string format for representing chemical structures\textsuperscript{42}. For each C19-CTD, the structure in SMILES format was extracted from the DrugBank XML file. The ChEMBL API library (written in python) was used to obtain a list of structurally similar drugs (SSDs). The ChEMBL structural similarity tool uses the Tanimoto coefficient (Tc) to predict structural similarity.

Filtering the list of SSDs

The list of SSDs was refined to remove drugs which fell into several categories (Figure 2. Drug structural similarity screening (A) Histogram showing the number of drugs in Phase II+ with a Tc > 40 similar to C19-CTDs. The cut off for similarity of 70 is shown by the blue dashed line. The red box highlights the drawn structures (B-L). Heatmap of the chemical structures of the top 10 SSDs by similarity showing their structural similarity to C19-CTDs from which they were predicted. The structural differences are highlighted in red. (B) Tafimoxifen predicts Afimoxifene. (C) Verapamil predicts Gallopamil. (D) Sirolimus predicts (E) Everolimus, (F) Ridaforolimus, (G) Temirolimus, and (H) Zotarolimus. (I) Dexamethasone predicts Triamcinilone. (J) Icosapent predicts Docosapentaenoic acid. (K) Amoxicillin predicts Ampicillin. (L) Mannitol predicts Xylitol.) as follows: SSDs that were in Phase II clinical trials or higher for any condition were retained at this stage because they passed Phase I trials and have therefore been tested for safety in humans. Tc > 70 was used as a similarity cut off. For context, a threshold of 70-75 is typical for structure based screening\textsuperscript{43}. 
The list of SSDs was cleaned to remove effective duplicates that behave the same in the body despite of a slightly different chemical structure.

**Drug target filtering**

We used the SARS-CoV-2-induced protein (SIP) network at 24 hours generated by Han et al\textsuperscript{19} as the base network to investigate the COVID-19 pathways on which these structurally similar drugs (SSDs) are acting. Briefly, this network contains the directly interacting proteins (DIP) of SARS-CoV-2 identified by mass spectrometry\textsuperscript{20}, differentially expressed proteins (DEP) after infection by SARS-CoV-2 identified by mass spectrometry\textsuperscript{21}, and a layer of connections between the two built using known protein-protein interaction (PPI) data as described in the Han et al paper\textsuperscript{19}.

**Drug-target interactions**

Drug-target interaction information was collected from DrugBank(v 5.1)\textsuperscript{44} and STITCH(v 5.0, confidence score > 0.8)\textsuperscript{45}.

**Distance between targets of SSD and the targets of C19-CTD**

We define the distance $d_C(S, C)$ between $S$, the set of target proteins of a SSD, and $C$, the set of target proteins of a C19-CTD, as the shortest path length $d(s, c)$ between all pairs of nodes $s \in S$ and $c \in C$ in the SIP 24-hour network\textsuperscript{19}. Closest distance measure (equation (1)) was used to calculate the distance between a SSD’s target to a C19-CTD’s target in the SIP 24-hour network because it showed the best performance in drug-drug relationship prediction in a study by Cheng et al\textsuperscript{46}.

\[
 d_C(S, C) = \frac{1}{|C|} \sum_{c \in C} \min_{s \in S} d(s, c) \quad (1)
\]
Drug-pathway associations

To identify key pathways that are significantly enriched in the proteins that are targeted by 28 SSDs and C19-CTDs, we conducted pathway enrichment analysis using R (v 3.5.2) package and gprofiler2\textsuperscript{47} (hypergeometric test, FDR-BH< 0.05). Reactome pathways (the version as of 15/05/2020) were used for pathway enrichment analysis because it is the most actively updated public database of human pathways\textsuperscript{48}. Pathway enrichment analysis was performed for each of the 28 drugs. The number of target proteins of the 28 drugs are from two to 125. The average number of target proteins of the 28 drugs are 14. Drugs targeting fewer than six proteins have no significantly enriched pathways. To overcome this problem, if drugs have less than 14 target proteins, which is the average number of target proteins, neighbour proteins of the target proteins in the SIP 24-hour network are added up to 14 proteins. Significantly enriched biological pathways of target proteins for each of the 28 drugs were integrated, resulting in 488 key pathways. The Reactome pathway has a hierarchical structure among pathways. The lower hierarchy pathway is more specific than the higher hierarchy pathway. The parent pathway semantically includes its child pathways. In the process of integrating the enriched pathways per drug, we used the lowest-possible hierarchy pathways to avoid the overlapping biological meaning among the hierarchical pathways.

Based on these identifications, a matrix containing F1 scores of the 28 drugs and the 488 key pathways was generated for drug-pathway association. The Reactome pathway enrichment analysis for the 28 drugs using gprofiler2 provides enrichment p-values, precision and recall information that were used to produce the F1 scores. The meaning of precision here is that the proportion of drug targets that are annotated to the pathway. The meaning of recall here is that the proportion of the pathway gene sets that the drug targets recover. Precision and recall were used to construct a matrix of F1 score (F1=2(precision \times recall)/(precision + recall)) from the pathway enrichment analysis.
**In silico MoA analysis**

To identify mechanism of action (MoA) for Triamcinolone and Gallopamil in COVID-19 we identified their relationships within the SIP 24-hour SARS-CoV-2 network. There are 14,827 proteins and 528,969 interactions in this network. Bouhaddou et al.\textsuperscript{26} predicted kinase activities in the first 24h post infection with SARS-CoV-2 based on the regulation of their known substates. From their data we used all kinases with activity absolute LogFC > 1.5 at any time point in the first 24h post infection for verification as these are being activated in early SARS-CoV-2 infection. To estimate the proximity of the targets of the drugs of interest to these active kinases in the SIP network, we calculated the distance of each target to each kinase and took the average of these distances. To establish significance, we did a permutation test. Each drug had 3 targets in the network, so we randomly generated 10,000 groups of 3 proteins and calculated the average distance of these from the active kinases (Figure 4A). We used closest 5% distances as a cut off to establish significance. To visualise the target proteins interacting with these kinases and other key COVID-10 proteins, we plotted subnetworks using Virtualitics Immersive Platform\textsuperscript{49}.

**Target proteins of drugs expression change in COVID-19 patient data**

To validate the effects of two drugs indirectly, Triamcinolone and Gallopamil, we checked whether the target proteins of drugs are significantly changed between patients with moderate COVID-19 and patients with severe COVID-19 when the expression of these targets is compared to expression of random proteins. Arunnachalam et al.\textsuperscript{27} provide Log2 fold change of gene expression between 4 COVID-19 moderate patients verse 12 COVID-19 severe patients. In Figure 4C boxplot, only the proteins belonging to the HDL remodelling pathway among the neighbour proteins of each of the drugs target proteins in SIP 24-hour network and randomly selected control proteins were compared. Among the target proteins and their neighbour proteins, the same number of proteins in the HDL remodelling pathway were randomly selected. This random choice was repeated 100 times to create control proteins. For example, if five of the target proteins and their neighbour proteins belong to the
HDL remodelling pathway, 500 proteins were randomly selected and made into control proteins. The Mann Whitney U test was performed to determine whether the expression two groups were significantly different between moderate and severe COVID-19 patients.

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Author contributions
Conceptualization, M.M. and W.H.; Methodology, M.M., W.H. and N.H.; Software, M.M., W.H. S.Y., M.T. and N.H.; Validation, M.M., W.H. and N.H.; Formal Analysis, M.M., W.H. and N.H.; Investigation, M.M, W.H., N.H., S.Y., E.M., A.A., J.B., M.T., P.B., and, V.P.G.; Resources, N.H.; Data Curation, M.M., W.H., E.M. and N.H.; Writing – Original Draft M.M. and W.H.; Writing- Review and editing M.M, W.H., N.H., S.Y., E.M., A.A., J.B., M.T., and, V.P.G.; Visualization, M.M., W.H., E.M., and N.H; Supervision, N.H.; Project Administration M.M., W.H. and N.H.

Declaration of interests
MM is an employee of LifeArc. NH and WH are funded by LifeArc. NH is a co-founder of KURE.ai and an advisor at Biorelate, Promatix, and Standigm. All other authors declare that they have no competing interests.

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Figure legends

Figure 1. Overview of SSD prediction and filtering showing the number of drugs retained after each filtering step.

Figure 2. Drug structural similarity screening (A) Histogram showing the number of drugs in Phase II+ with a Tc > 40 similar to C19-CTDs. The cut off for similarity of 70 is shown by the blue dashed line. The red box highlights the drawn structures (B-L). Heatmap of the chemical structures of the top 10 SSDs by similarity showing their structural similarity to C19-CTDs from which they were predicted. The structural differences are highlighted in red. (B) Tafimoxifen predicts Afimoxifene. (C) Verapamil predicts Gallopamil. (D) Sirolimus predicts (E) Everolimus, (F) Ridaforolimus, (G) Temirolimus, and (H) Zotarolimus. (I) Dexamethasone predicts Triamcinilone. (J) Icosapent predicts Docosapentaenoic acid. (K) Amoxicillin predicts Ampicillin. (L) Mannitol predicts Xylitol.

Figure 1. Drug-pathway association study (A) 21 SOM component plane heatmaps. In each plane heatmap, the hexagon in a certain position corresponds to a set of unique pathways which has the same position across all heatmaps (drugs). Each hexagon is coloured according to the distance between corresponding data vectors of neighbour neurons, with low distances areas (bright yellow) indicating high data density. Mapping of the 21 drugs to each neuron (pathway) based on matching rates and inspection of examples from each cluster (1-8). (B) Unified distance matrix (U-matrix) of SOM result. (C) Principal component (PC) projection of SOM represents the distribution of trained neurons in the data space. (D) Colour code of SOM grid shows the clustering information and the number of hits (pathways) in each hexagon (neuron) (E) Davies-Bouldin index (DBI) indicates that 10 is the optimal number of clusters. (F) 10 pathway clusters and their names.

Figure 2. In silico validation of Gallopamil and Triamcinilone. (A) Histogram of average distances between 10,000 groups of 3 proteins and kinases active in SARS-COV-2
infection. The distance of the Gallopamil and Triamcinolone targets are indicated with arrows, and the red dashed line shows the permutation cut-off for the 5% of protein groups closest to the kinases (p-value = 0.05) (B) Subnetwork of Gallopamil and Triamcinolone target proteins and their direct interactors which are important in COVID-19 infection. (C) Boxplots showing fold-change in moderate patients with covid-19 of a target protein of the drug and neighbour proteins of the target protein. The control results in the boxplot show fold-change of random genes with the same number of a target protein and the neighbour proteins of the target protein. Significance was tested by the Mann Whitney U test (p-value <0.05).
Available compounds in Clinical Trial Phase 2, 3 and 4 (Approved)

7,682

78

101

73

17

12

2

Screen structurally similar drugs with 185 drugs in COVID-19 clinical trials

Remove effective duplicates

Remove antineoplastic agents due to adverse drug reactions

Remove close proximity or identical targets on SIP network

Remove similar MoA based on pathway clustering by SOM

Retain viral replication-associated MoA
Structural similarity (Tc) Number of drugs phase 2 or above

| C19-CTD  | Tc   | SSD  |
|----------|------|------|
| Tamoxifen| 89.74| Afimoxifene |
| Sirolimus| 87.27| Everolimus |
| Sirolimus| 87.27| Ridaforolimus |
| Verapamil| 86.54| Gallopamil |
| Dexamethasone| 85.96| Triamcinolone |
| Icosapent| 85.19| Docosapentaenoic Acid |
| Sirolimus| 84.21| Temsirolimus |
| Amoxicillin| 84.00| Ampicillin |
| Sirolimus| 83.48| Zotarolimus |
| Mannitol| 83.33| Xylitol |
A

Average distance from simulated target groups to active kinases

p=0.05

B

Gallopamil Subnetwork

Triamcinolone Subnetwork

C

Gallopamil Targets

Triamcinolone Targets

DIP

Kinase Active

Drug Target

HDL Remodelling Pathway