Large-scale ligand-based virtual screening for SARS-CoV-2 inhibitors using deep neural networks

Markus Hofmarcher [1 2 *] **Andreas Mayr** [1 2 *] **Elisabeth Rumetshofer** [1 2 *] **Peter Ruch** [1 2 *] **Philipp Renz** [1 2 *] **Johannes Schimunek** [1 2 *] **Philipp Seidl** [1 2 *] **Andreu Vall** [1 2 *] **Michael Widrich** [1 2 *] **Sepp Hochreiter** [1 2 *] **Günter Klambauer** [1 2 *]

Abstract

Due to the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, there is an urgent need for novel therapies and drugs. We conducted a large-scale virtual screening for small molecules that are potential CoV-2 inhibitors. To this end, we utilized "ChemAI", a deep neural network trained on more than 220M data points over 3.6M molecules from three public drug-discovery databases. With ChemAI, we screened and ranked one billion molecules from the ZINC database for favourable effects against CoV-2. We then reduced the result to the 30,000 top-ranked compounds, which are readily accessible and purchasable via the ZINC database. We provide these top-ranked compounds as library for further screening with bioassays at https://github.com/ml-jku/sars-cov-inhibitors-chemai.

Introduction. Due to the current world-wide crisis of SARS-CoV-2 virus infections, there is a strong need for new therapies. While many efforts are focused on repurposing existing drugs (Zhou et al., 2020; Wang et al., 2020; Ton et al., 2020), we suggest to test new molecules with potentially higher efficacy. To this end, we performed a large-scale ligand-based virtual screening run, which resulted in 30,000 potential SARS-CoV-2 inhibitors with favorable properties. We actively outreach to the scientific community to test these molecules and consider them as a custom-designed chemical library.

Most current virtual screens are structure-based and use docking methods (Chen et al., 2020; Huang et al., 2020; Haider et al., 2020; Wang et al., 2020; Fischer et al., 2020; Chen et al., 2020; Ton et al., 2020; Senathilake et al., 2020; Ruan et al., 2020; Jin et al., 2020; Zhang et al., 2020) while one is ligand-based and uses a similarity-based approach (Zhu et al., 2020). The largest docking studies screen databases with sizes ranging from roughly 700M (Fischer et al., 2020) to 1.3 billion (Ton et al., 2020) molecules. We as well operate in this range by screening a collection of one billion molecules from the ZINC database.

Deep ligand-based virtual screening. ChemAI is a deep neural network trained to simultaneously predict a large number of biological effects (Mayr et al., 2018; Preuer et al., 2019). Concretely, the network is trained on a data set comprised ChEMBL (Gaulton et al., 2017), ZINC (Sterling & Irwin, 2015) and PubChem (Kim et al., 2016), and which is similar to the data set used by Preuer et al. (2018). The network, called "ChemAI", predicts in total 6,269 biological outcomes, such as binding to targets, inhibitory or toxicity effects. The network was trained in a multi-task setting, in which data from other bioassays is used to enhance the predictive power for SARS-CoV inhibitory effects. Each modelled biological effect is represented by an output neuron of the neural network. We utilized a small set of output neurons associated with SARS-CoV inhibition and a set of output neurons associated with toxic effects to rank compounds.

We screen the ZINC database because it provides a large set of diverse molecules and offers a link to vendors such that those molecules can readily be bought and obtained physically. We downloaded roughly 1 billion molecules from ZINC and converted them to canonical SMILES (Weininger, 1988) using RDKit (Landrum, 2006). We then performed inference with the network ChemAI to obtain predictions for each of those 1 billion molecules.

Bioassays. The SARS-CoV-2 has two main proteases that are critical for its replication, these are the 3CLpro(3C-like protease) and PLpro(Papain Like Protease) encoded by the open reading frame (Macchiagodena et al., 2020). A compound that inhibits both proteases (Ledford, 2009; Collison, 2019) could be a promising drug candidate. The

[*]Equal contribution [1]ELLIS Unit at the LIT AI Lab, Johannes Kepler University Linz, Austria [2]Institute for Machine Learning, Johannes Kepler University Linz, Austria. Correspondence to: Günter Klambauer <klambauer@ml.jku.at>.

Technical Report

Assay ID	Source	#inact	#act	Description
1706	PubChem	193637	269	QFRET-based assay for SARS-CoV 3C-like Protease
1879	PubChem	167	86	QFRET-based assay for SARS-CoV 3C-like Protease (confirmation)
485353	PubChem	215030	390	Yeast-based Assay for SARS-CoV PLP
652038	PubChem	493	135	Yeast-based Assay for SARS-CoV PLP (validation)

Table 1. Overview of the main biological effects considered for ranking the molecules of the virtual screen. "#inact" and "#actAll" report the number of actives and inactives in the training set. All assays are based on inhibition of proteins of SARS-CoV-1.

proteases are also strikingly similar to those in SARS-CoV-1 (Macchiagodena et al., 2020), which is also an implicit assumption by docking-based approaches. We therefore select two groups of assays of which one measures the inhibition of 3CLpro and the other the inhibition of PLpro (see Table 1). For each of those four assays, ChemAI possesses an output unit, which models the ability of small molecules to exhibit the effect measured by the assay. Thus, using the predictions by ChemAI, it is possible to rank compounds by their predicted ability to inhibit the two main proteases of SARS-CoV-1, which can be a proxy for the inhibitory potential for SARS-CoV-2.

Consensus ranking. We developed a compound library which is enriched for molecules with the ability to inhibit both proteases of the SARS-CoV-2. For scoring the multi-target effect, we calculated a consensus score for each molecule as the average rank of the predictions in each of the four selected assays (see Table 1). We then ranked all compounds by this consensus score. For each of the top-ranked compounds, we also calculated their minimal distance to actives in the training set to be able to identify novel chemical structures. We also report the number of potential toxic effects of a compound (Mayr et al., 2016).

We implemented the overall process as a two-step approach. In the first step, we reduced the ZINC database of 1 billion molecules to a smaller set, where we kept all molecules that exhibited some predicted activity on any of the four assays, i.e. at least one of the predictions had to reside in the top-1% quantile. In this way, we obtained an intermediate dataset of 5,672,501 molecules. For those molecules, the consensus score, the toxicity-flags and the distance to known actives were calculated. In the second step, we reduced the dataset to the top-ranked 30,000 molecules by the consensus score.

Results. With the abovementioned approach, we have assembled a library of potential inhibitors of SARS-Cov-2. For each compound, we report three metrics for each compound: a) predicted inhibitory effect of SARS-CoV proteases b) potential toxicities and c) distance to known actives. This led to a ranked list of compounds of which we provide the top 30,000 as a screening library. The top-ranked molecules are given in Table 2 and Figure 1.

We also checked whether molecules suggested by other publications can be confirmed by ChemAI. Overall, some suggested molecules show at least mild predicted activity against SARS-CoV (see Table 3).

Discussion. In this work, we presented the construction of a screening library of small molecules that are potential inhibitors of SARS-CoV-2. Our ligand-based approach uses a neural network trained to predict the outcomes of bioassays. From this multi-task models, four tasks have been selected to predicting the inhibitory potential against SARS-CoV-1. A consensus between these predictions was used to rank compounds from the ZINC database, of which the 30,000 top-ranked are reported.

The approach is limited by the predictive quality of the underlying machine learning method, evaluated via the area-under-ROC-curve leading to values in the range of 0.69 to 0.78. While these results are very promising, improved data quality, amount of data or other machine learning approaches could lead to increased predictive performance and hence library. We expect that the data for SARS-CoV-1 already has high predictive power for inhibitory effects of compounds on SARS-CoV-2. However, the current predictions can be further adjusted toward SARS-CoV-2 via transfer-learning and incorporating new data from SARS-CoV-2. In particular few shot learning may be utilized for the first measurements for SARS-CoV-2 which will adjust the multi-task model toward SARS-CoV-2

Availability The library of molecules is available at `https://github.com/ml-jku/sars-cov-inhibitors-chemai`.

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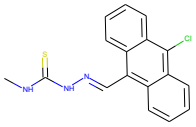

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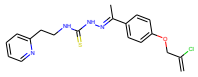

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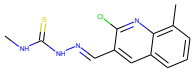

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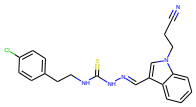

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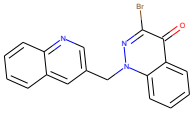

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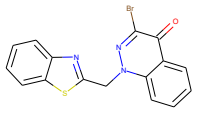

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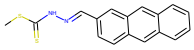

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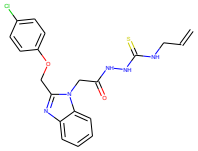

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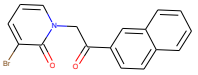

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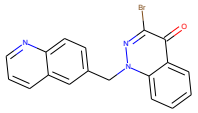

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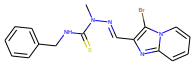

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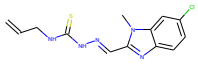

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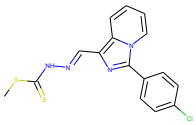

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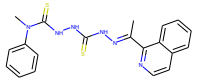

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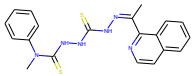

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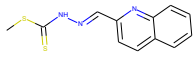

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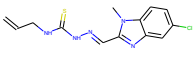

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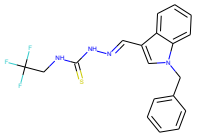

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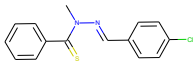

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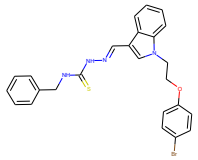

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Figure 1. Graphical representation of the top-ranked molecules by ChemAI.

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ZINC000726422572	C=C(Cl)COc1ccc(C(C)=NNC(=S)NCCc2ccccn2)cc1	0.5333	0.8232	7
ZINC000916265995	CNC(=S)NN=Cc1cc2cccc(C)c2nc1Cl	0.6111	0.8230	5
ZINC000916356873	N#CCCn1cc(C=NNC(=S)NCCc2ccc(Cl)cc2)c2ccccc21	0.6377	0.8221	17
ZINC000806591744	O=c1c(Br)nn(Cc2cnc3ccccc3c2)c2ccccc12	0.7258	0.8215	11
ZINC000178971373	O=c1c(Br)nn(Cc2nc3ccccc3s2)c2ccccc12	0.7288	0.8211	8
ZINC000000155607	CSC(=S)N/N=C/c1ccc2cc3ccccc3cc2c1	0.3902	0.8204	4
ZINC000016317677	C=CCNC(=S)NNC(=O)Cn1c(COc2ccc(Cl)cc2)nc2ccccc21	0.7000	0.8197	4
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ZINC000769846795	O=c1c(Br)nn(Cc2ccc3ncccc3c2)c2ccccc12	0.6949	0.8195	9
ZINC000755523869	CN(N=Cc1nc2ccccn2c1Br)C(=S)NCc1ccccc1	0.6452	0.8194	4
ZINC000763345954	C=CCNC(=S)NN=Cc1nc2ccc(Cl)cc2n1C	0.6508	0.8194	5
ZINC000001448699	CSC(=S)N/N=C/c1nc(-c2ccc(Cl)cc2)n2ccccc12	0.6866	0.8192	4
ZINC000016940508	C/C(=N\NC(=S)NNC(=S)N(C)c1ccccc1)c1nccc2ccccc12	0.6721	0.8191	11
ZINC000005486767	C/C(=N/NC(=S)NNC(=S)N(C)c1ccccc1)c1nccc2ccccc12	0.6721	0.8191	11
ZINC000005527649	CSC(=S)N/N=C/c1ccc2ccccc2n1	0.6327	0.8187	6
ZINC000755497029	C=CCNC(=S)NN=Cc1nc2cc(Cl)ccc2n1C	0.6719	0.8186	5
ZINC000746495682	FC(F)(F)CNC(=S)NN=Cc1cn(Cc2ccccc2)c2ccccc12	0.5690	0.8186	15
ZINC000005719506	CN(/N=C/c1ccc(Cl)cc1)C(=S)c1ccccc1	0.6818	0.8178	4
ZINC000002149503	S=C(NCc1ccccc1)N/N=C/c1cn(CCOc2ccc(Br)cc2)c2ccccc12	0.5625	0.8175	13

Table 2. Top-ranked molecules found by ChemAI. All compounds have a predicted high activity on all four assays (column "score") and are relatively distant (column "dist") to current known inhibitors. Some of the presented molecules might exhibit a number of toxic effects (column "tox").

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ZINC-ID	Trivial-Name(s)	Canonical Smiles	Publications
ZINC00057060	Melatonin	COc1ccc2[nH]cc(CCNC(C)=O)c2c1	Zhou et al. (2020)
ZINC03869685	Meletin, Quercetin	O=c1c(O)c(-c2ccc(O)c(O)c2)oc2cc(O)cc(O)c12	Lim et al. (2016)
ZINC85537142	Aclarubicin	CC[C@@]1(O)C[C@H](O[C@H]2C[C@H](N(C)C)[C@H](O[C@H]3C[C@H](O)[C@H](O[C@H]4CCC(=O)[C@H](C)O4)[C@H](C)O3)[C@H](C)O2)c2c(cc3c(c2O)C(=O)c2c(O)cccc2C3=O)[C@H]1C(=O)OC	Senathilake et al. (2020)
ZINC03794794	Mitoxantrone	C1=CC(=C2C(=C1NCCNCCO)C(=O)C3=C(C=CC(=C3C2=O)O)O)NCCNCCO	Wang et al. (2020)
ZINC01668172	-	O=C(C[n+]1ccc2ccccc2c1)c1ccc2ccc3ccccc3c2c1	Glantz-Gashai et al. (2017)
ZINC03830332	E155	C1=CC=C2C(=C1)C(=CC=C2S(=O)(=O)O)NN=C3C=C(C(=O)C(=NNC4=CC=C(C5=CC=CC=C54)S(=O)(=O)O)C3=O)CO	Senathilake et al. (2020)
ZINC14879972	Gar-936	CN(C)c1cc(NC(=O)CNC(C)(C)C)c(O)c2c1C[C@H]1C[C@H]3[C@H](N(C)C)C(O)=C(C(N)=O)C(=O)[C@@]3(O)C(O)=C1C2=O	Wu et al. (2020)
ZINC00001645	Magnolol	C=CCc1ccc(O)c(-c2cc (CC=C)ccc2O)c1	Wu et al. (2020)
ZINC00014036	Piceatannol	Oc1cc(O)cc(/C=C/c2ccc(O)c(O)c2)c1	Wu et al. (2020)
ZINC16052277	Doxycycline	C[C@H]1c2cccc(O)c2C(=O)C2=C(O)[C@]3(O)C(=O)C(C(=N)O)=C(O)[C@@H](N(C)C)[C@@H]3[C@@H](O)[C@@H]21	Wu et al. (2020)
ZINC3920266	Idarubicin	CC(=O)[C@]1(O)Cc2c(O)c3c(c(O)c2[C@@H](O[C@H]2C[C@H](N)[C@H](O)[C@H](C)O2)C1)C(=O)c1ccccc1C3=O	Wu et al. (2020)

Table 3. Compounds suggested in related publications for potential activity against SARS-CoV-2 and which also exhibit at least mild predicted activity against and SARS-CoV proteases by ChemAI.