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Research Paper

AI drug discovery screening for COVID-19 reveals zafirlukast as a repurposing candidate☆

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ABSTRACT

Aims: Over the past few years, AI has been considered as potential important area for improving drug development and in the current urgent need to fight the global COVID-19 pandemic new technologies are even more in focus with the hope to speed up this process. The purpose of our study was to identify the best repurposing candidates among FDA-approved drugs, based on their predicted antiviral activity against SARS-CoV-2.
Materials and methods: This article describes a drug discovery screening based on a supervised machine learning model, trained on *in vitro* data encoded in chemical fingerprints, representing particular molecular substructures. Predictive performance of our model has been evaluated using so-called scaffold splits offering a state-of-the-art setup for assessing model's ability to generalize to new chemical spaces, critical for drug repurposing applications.
Key findings: Our study identified zafirlukast as the best repurposing candidate for COVID-19.
Significance: Zafirlukast could be potent against COVID-19 both due to its predicted antiviral properties and its ability to attenuate the so called *cytokine storm*. Thus, these two critical mechanisms of action may be combined in one drug as a novel and promising pharmacotherapy in the current pandemic.

1. Introduction

Severe acute respiratory syndrome coronavirus SARS-CoV-2 emerged in Wuhan, Hubei province in China in late 2019. The pandemic was announced by WHO on March 11, 2020, with nearly 46 million COVID-19 cases and 1.2 million deaths till the moment of writing this article [1,2]. Due to the devastating effects associated with pandemic coronavirus outbreaks, both new prophylactic and therapeutic interventions are urgently needed to be developed [3]. It is well known that the success rate for drug development (as defined from phase I clinical trials to drug approvals) is very low, reaching about 6.2% [4,5] and the process takes typically 12 to 15 years [6]. Hence, drug repurposing or repositioning has become a promising approach due to the opportunity to significantly reduce both development time and costs. Over the past few years, *in silico* artificial intelligence (AI) and machine learning (ML) techniques have been considered as important areas for driving improvements in drug development [4] and in the current urgent need to fight the global COVID-19 pandemic new technologies are even more in focus with the hope to speed up this process and find new therapeutic indications [7–15), bearing in mind that *in silico* results are still subject to additional *in vitro* and *in vivo* experiments and further clinical trials that are needed to ensure the efficacy of the proposed drugs [16].

The novel virus belongs to the family of *Coronaviridae* and exploits ACE2 receptors for entry, suggesting that the virus might target a similar spectrum of cells as SARS-CoV [17]. The symptoms of COVID-19 at the onset of illness include fever, cough, myalgia or fatigue, sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. Patients develop pneumonia with abnormal findings on chest CT while the complications include acute cardiac injury, acute respiratory distress syndrome, and secondary infections as well as *cytokine storm* that may be associated with disease severity [18,19]. As the sequence identities of SARS-CoV-2 3CL protease (3CLpro), RNA polymerase, and the spike protein with corresponding SARS-CoV proteins are 96.08%, 96%, and 76%, respectively [20], one may suggest the implementation of drugs that are effective against SARS-CoV for the treatment of SARS-CoV-2 infection. Nevertheless, regarding the potentially increased transmissibility of SARS-CoV-2 in comparison to SARS-CoV, it seems that the new virus uses attachment-promoting factors in cells more effectively than SARS-CoV [17], yet with more effective immune surveillance evasion for SARS-CoV-2 than in case of SARS-CoV [21].

Related work in the context of *in silico* AI and ML applications for identifying drug candidates for the treatment of SARS-CoV-2 is still scarce, but with the increasing importance of this area, new research efforts are being invested in this direction. Similar studies published so far indicated,

☆ The views expressed in this article are those of the authors and not necessarily those of Erste Group IT.

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among others, phenazopyridine, abemaciclib, promazine, tyverb, pirenzepine, ebastine, and alectinib [22], atazanavir, remdesivir, and efavirenz [11] as well as vismodegib, gemcitabine, clofazimine, celecoxib, brequinar, conivaptan, bedaquiline, tolcapone, and pranlukast [9]. The potential use of some of these repurposing candidates against COVID-19 is also widely discussed in review and commentary articles, as it is in the case of leukotriene receptor antagonists (LTRAs) [23,24].

The purpose of our study was to identify the best repurposing candidates among the Food and Drug Administration (FDA)-approved drugs, based on their predicted antiviral activity against SARS-CoV-2. The FDA-approved drugs constitute a good starting point in the context of repurposing officially approved and safe drugs against COVID-19 [15]. To this end, we have trained a supervised machine learning model based on gradient-boosted tree ensembles, operating on *in vitro* data encoded in chemical fingerprints, representing particular molecular substructures.

2. Materials and methods

2.1. Datasets

The dataset used to train our model consists of ~290,000 negative and 405 active molecules from the primary biochemical high throughput screening assay for identification of the SARS-CoV 3CLpro inhibitors [25]. Due to the fact that SARS-CoV 3CLpro is an integral component in the viral replication process and exhibits above 96% sequence identity to the SARS-CoV-2 3CLpro [19], the considered dataset composes to our knowledge the largest currently available sample of this type, on which an ML model can be trained to provide predictions for inferring the antiviral activity against SARS-CoV-2. The purpose of the primary biochemical screening assay was to identify compounds that inhibit SARS-3CLpro-mediated peptide cleavage. A fluorescent compound, which is attached to the N-terminus of a 3CLpro peptide substrate, is quenched by a moiety attached at the C-terminus. When enzyme is active, the peptide is cleaved by 3CLpro and the fluorescent compound and quencher separate, leading to an increase in well fluorescence (excitation wavelength of 485 nm and an emission wavelength of 535 nm). Compounds added to these wells are tagged as inactive (antiviral activity is negative). Compounds that inhibit 3CLpro activity prevent cleavage of the labeled peptide substrate, resulting in no increase in fluorescence. These compounds are tagged as active (antiviral activity is positive).

Although the utilized dataset comprises activity toward SARS-CoV 3CLpro, exhibiting above 96% sequence identity to the SARS-CoV-2 3CLpro, in addition to the original dataset [25], we consider also a manually curated version of the same dataset, based on the following enrichment. We added to the dataset the following known SARS-CoV-2 3CLpro inhibitors[1] as active molecules, based on the already published results: ebselen, disulfiram, tideglusib, carmofur, shikonin, PX-12 [26], ritonavir [27], lopinavir, teicoplanin, oseltamivir, nitazoxanide, hydroxychloroquine, famciclovir, chloroquine, azithromycin, atazanavir, amoxicillin, aciclovir [28], and quercetin [29].[2]

As a screening set of molecules, among which the best repurposing candidates are sought after based on their predicted antiviral activity against SARS-CoV-2, we used the FDA set of all approved drugs *FDA Approved drugs, per DrugBank* [30]. The list of FDA-approved drugs serves as an important resource for medical practice and represents compounds that are safe and efficacious drug products as well as their generic equivalents, approved by the FDA for use in the United States [31].

[1] As known SARS-CoV-2 3CLpro inhibitors we treat only those, for which published results based on laboratory experiments are confirming the inhibition.

[2] Since the following 5 drugs: ebselen, disulfiram, nitazoxanide, famciclovir, and aciclovir are included in the original dataset as inactive molecules and they are according to current research considered as already known SARS-CoV-2 3CLpro inhibitors [26,28], in the manually curated version of the dataset we inlcude them as active molecules.

2.2. Machine learning model

Regarding AI and ML technologies applicable to molecular property prediction, in general, two categories of models can be considered: models operating on precomputed molecular fingerprints and deep neural networks constructing their own chemical representations, and it remains an open research area to find out which of the two paradigms is superior for which predictive task and for which characteristics of the data at hand [4,32].

The approach applied in this study to molecular property prediction for drug discovery is based on MACCS fingerprints computed using RDKit library [33] and an implementation of a gradient-boosted tree learning method (XGBoost [34]), ensembling in sequential manner individual tree models, partitioning the space of molecular fingerprints. The prediction of a gradient-boosted tree ensemble is given as a combined consensus prediction based on a large number of tree models grown in a forward-stagewise manner. The ensemble model is greedily updated by adding new trees that, by addressing the weaknesses of the previous ensemble, most improve the overall model. An illustrative overview of our approach is given in Figure 1.

As one of the challenges in training a machine learning model on the data at hand is its imbalanced character, we performed additional experiments with the following approaches: undersampling of the inactive class, oversampling of the active class using the SMOTE method [35] as, well as tuning a hyperparameter weighting the balance of active relative to inactive molecules for scaling the gradient for the active class, when ensembling the decision trees. However, as these attempts did not lead to improved performance in terms of AUC, we did not use them in the final model training.

2.3. Evaluation method

For assessing the quality of the classifier outputs, we used Receiver Operating Characteristic curve-Area Under the Curve (ROC-AUC) as the primary metric. Predictive performance of our model was evaluated based on repeated random subsampling cross-validation using 10 randomly seeded 80:20 scaffold splits of training and testing data. Compared to commonly used random splits, the utilized scaffold splits offer a superior and more challenging setup for assessing model's ability to generalize to new chemical spaces, critical for drug repurposing applications [32]. More specifically, in order to ensure that the models' capacity to generalize to new molecular structures is tested on compounds that are structurally different from those used in the training phase, we follow the scaffold splitting approach [32,36] and divide all molecules into partitions based on their Murcko scaffolds calculated using RDKit. Partitions with molecule count that would exceed the half of the desired test set size are allocated to the train set and the remaining partitions are randomly allocated to the train and test sets, until the desired split ratio is achieved.

2.4. Generating final predictions

For generating the final predictions of the antiviral activity of the FDA-approved drugs, we have retrained our ensemble model on the whole dataset and used the predicted probabilities of activity for ranking the repurposing candidates. In order to reduce the inherent variability in model predictions due to stochastic nature of the algorithm, we have built a meta-ensemble consisting of 10 models, each trained with a different random seed. The final rank of each drug used for ordering the repurposing candidates was obtained by taking the median over individual rankings from the meta-ensemble.

3. Results

Under the evaluation scheme described in Section 2.3, our model achieved ROC-AUC of 0.72 ($\pm$0.03). Our top rank-ordered repurposing candidates with median rank less than 30 are provided in Table 1, showing next to the final median rank also the median absolute deviation (MAD) as a measure of variability of the rankings, as well as the median lethal dose

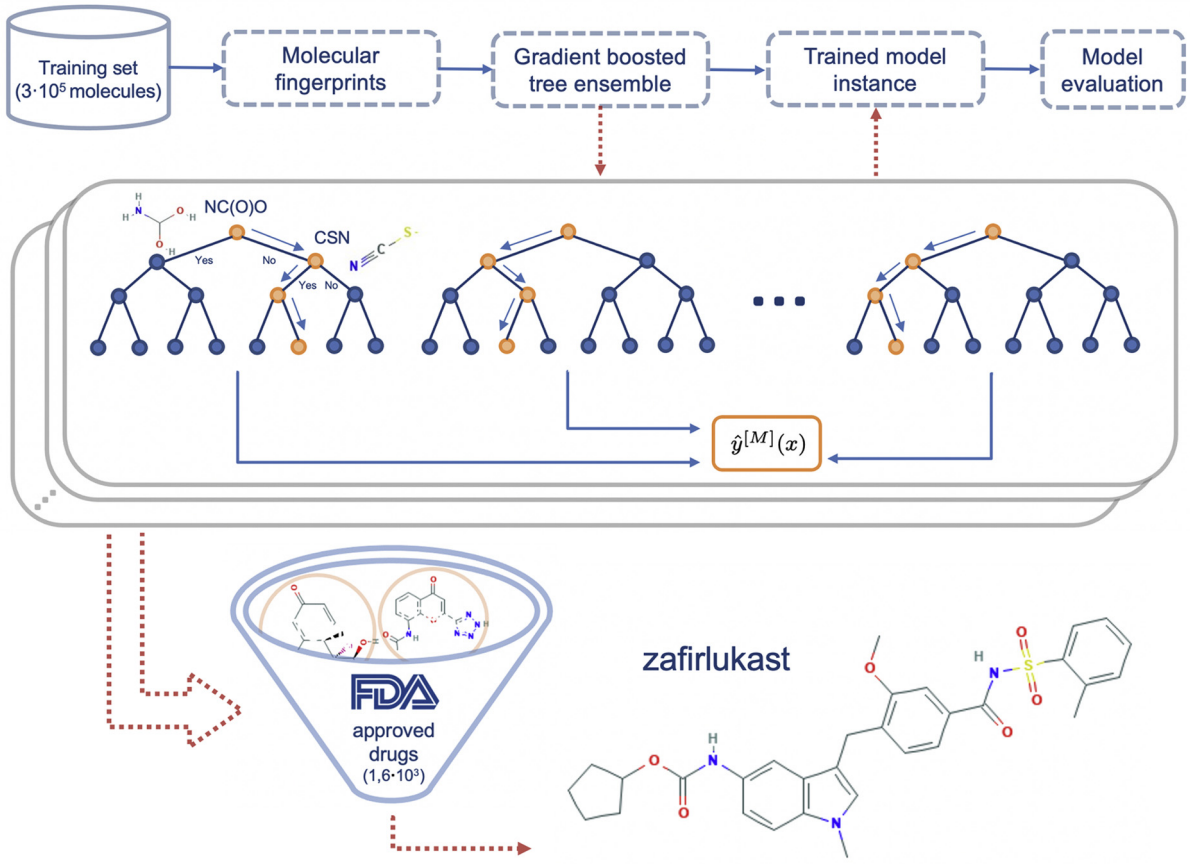

Figure 1. A schematic illustration of the described AI-based drug discovery screening for COVID-19.

(LD50) as a measure of drugs safety. The same list of 15 rank-ordered repurposing candidates is shown in Figure 2, illustrating the median ranks based on the meta-ensemble model together with the individual rankings used for calculating the final median rank. Table 2 provides the corresponding Anatomical Therapeutic Chemical (ATC) Classification System codes and characterizations of compounds class to which they belong.

We identified zafirlukast as the best repurposing candidate among all FDA-approved drugs, and it has been consistently ranked as number one by all constituents of our meta-ensemble, as visible in Figure 2. While zafirlukast is unanimously identified as the best repurposing candidate, the individual rankings for hexachlorophene (rank 2 in the rank-ordered list) and methoxsalen (rank 3) are also observed to be exceptionally stable, with MAD values of 0 and 1, respectively. The positions of drugs ranked below them as repurposing candidates are supported by visibly weaker signal, as indicated by both the levels of median ranks (*e.g.,* for the 4th in the rank-ordered list metolazone, the value of median rank is already 10), as well as the values of MAD showing an upward trend.

Nevertheless, we note that liothyronine (rank 5) and indomethacin (rank 13) are drugs which are already under clinical trials for COVID-19.

The results based on the manually curated version of the same dataset (see Section 2.1) show very close level of ROC-AUC of 0.71 ($\pm$0.03) and zafirlukast remains as the best ranked candidate (unchanged median rank of 1). Among the lower ranked drugs, compared to the ranking based on the original (noncurated) dataset, the following drugs remain in the top 15, at only slightly different positions: hexachlorophene, methoxsalen, liothyronine, levothyroxine, fluvastatin, diflunisal. Interesting drug candidates appearing additionally in the top 15, below zafirlukast, are erythromycin, ampicillin, clarithromycin, valacyclovir, ganciclovir, and valganciclovir.

An illustration of zafirlukast embedded in the chemical spaces of both the training dataset and the screening FDA dataset, together with their chemical relationships, is visualized in terms of t-Distributed Stochastic Neighbor Embeddings (t-SNE) in Figure 3.

Table 1
Rank-ordered repurposing candidates with median rank less than 30. Next to median rank based on the meta-ensemble model, we report also MAD indicating the level of variability of the rankings based on the individual constituents of the meta-ensemble. In the last column, we show the values of the median lethal dose (LD50) as a measure of safety of the repurposing candidates

ChEMBL ID	Drug name	Rank median	Rank MAD	LD50
CHEMBL603	Zafirlukast	1	0	2.5723
CHEMBL496	Hexachlorophene	2	0	2.4031
CHEMBL416	Methoxsalen	3	1	2.4054
CHEMBL878	Metolazone	10	3	1.8955
CHEMBL1544	Liothyronine	10	3	2.7082
CHEMBL1624	Levothyroxine	10	3	2.7082
CHEMBL109	Valproic acid	11.5	7	1.8543
CHEMBL104	Clotrimazole	16.5	4	2.7194
CHEMBL46403	Stearic Acid	17.5	9.5	1.3275
CHEMBL350239	Fluvastatin	18.5	14	2.9472
CHEMBL139	Diclofenac	22.5	7.5	3.6447
CHEMBL1444	Letrozole	23	5	1.9916
CHEMBL6	Indomethacin	27	21.5	4.0722
CHEMBL1648	Isradipine	27	10.5	2.3960
CHEMBL898	Diflunisal	28.5	9.5	2.7735

4. Discussion

Our results indicating zafirlukast as the best repurposing candidate against SARS-CoV-2 infection are intriguingly complementary to the study of Sanghai and Tranmer [33] and Funk et al. [38], who suggested the usefulness of another drug from the same group, namely montelukast. Similarly, Ke et al. [9] proposed pranlukast as a repurposing candidate. Hence, these studies, put together with our result, compose a very

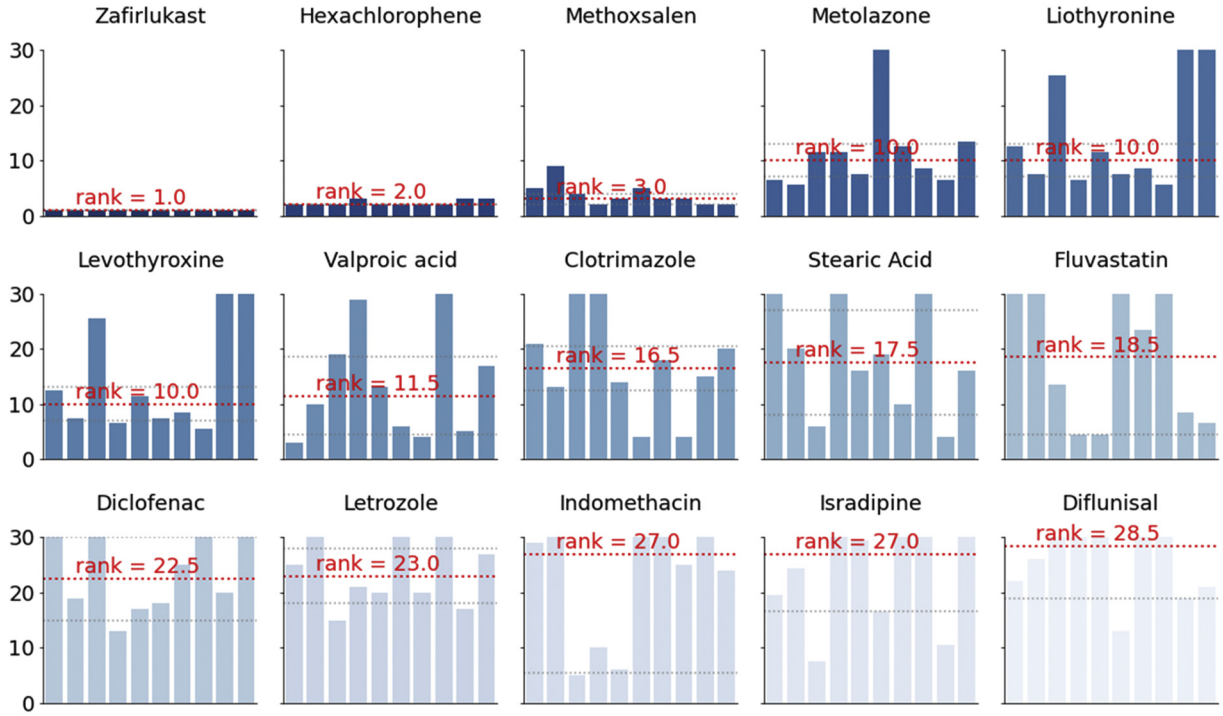

Figure 2. Rank-ordered repurposing candidates with median rank less than 30, based on the final meta-ensemble of 10 models and screening of all FDA-approved drugs. The bars correspond to individual ranks based on the constituents of the meta-ensemble, red dashed horizontal lines show the final median ranks and the gray dashed horizontal lines indicate the levels of variability of rankings around the median, taken as the median absolute deviation (MAD).

interesting compilation, drawing attention to the properties of leukotriene receptor antagonists as a potential treatment against COVID-19.

In addition to the remarkable complementarity of this result to the recent studies in the context of COVID-19 referenced above, we recall for a broader context also other, relevant pharmacological properties of zafirlukast and comment on them in relation to other LTRAs.

Zafirlukast is an oral LTRA for the treatment of asthma, available as a tablet and usually dosed twice daily. The undeniable advantage of zafirlukast, similarly to montelukast, is its safety. It is generally well tolerated, with a few associated adverse events [39]. Zafirlukast belongs to benzenesulfonamides, which contain a sulfonamide group that is S-linked to a benzene ring. Montelukast is a member of linear 1,3-diarylpropanoids, while pranlukast represents chromones, containing a benzopyran-4-one moiety. The structural diversity of these drugs seems not to impact their actually known mechanism of action. Zafirlukast blocks the action of the cysteinyl leukotrienes D4 and E4 on the cysteinyl leukotriene receptors (CysLT1), thus reducing inflammation, constriction of the airways and production of mucus in the lungs. Similarly, montelukast blocks the action of the cysteinyl leukotrienes C4, D4, and E4, while pranlukast selectively antagonizes leukotriene D4 at the CysLT1. The crucial impact of montelukast on COVID-19 includes attenuation of hyperinflammatory cytokine profile, termed as *cytokine storm*, through suppression of a protein complex (nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κB) [23], which is also a mechanism of action of zafirlukast [40]. The mentioned LTRAs may attenuate the activation of NF-κB transcription factor p50-p65, having impact on numerous genes expression and production of proinflammatory mediators involved in severe inflammation occurring in COVID-19 [23,38].

Table 2
Rank-ordered repurposing candidates with corresponding Anatomical Therapeutic Chemical (ATC) Classification System codes and characterization of compound class to which they belong

ChEMBL ID	Drug Name	ATC code	Compound class
CHEMBL603	Zafirlukast	R03DC01	benzenesulfonamides
CHEMBL496	Hexachlorophene	D08AE01	diphenylmethanes
CHEMBL416	Methoxsalen	D05BA02	methoxypsoralens
CHEMBL878	Metolazone	C03BA08	sulfonamides
CHEMBL1544	Liothyronine	H03AA02	phenylalanine and derivatives
CHEMBL1624	Levothyroxine	H03AA01	phenylalanine and derivatives
CHEMBL109	Valproic acid	N03AG01	methyl-branched fatty acids
CHEMBL104	Clotrimazole	D01AC01	triphenyl compounds
CHEMBL46403	Stearic Acid		long-chain fatty acids
CHEMBL350239	Fluvastatin	C10AA04	phenylpyrroles
CHEMBL139	Diclofenac	S01BC03	dichlorobenzenes
CHEMBL1444	Letrozole	L02BG04	diphenylmethanes
CHEMBL6	Indomethacin	S01BC01	benzoylindoles
CHEMBL1648	Isradipine	C08CA03	benzoxadiazoles
CHEMBL898	Diflunisal	N02BA11	biphenyls and derivatives

The antiviral properties of montelukast have been proposed in the study of Wu et al. [41], who predicted binding of the drug to the 3CLpro of SARS-CoV-2, with low binding energy. This finding suggests the antiviral property of the first LTRA representative against SARS-CoV-2. Moreover, according to the study of Almerie and Kerrigan [24], montelukast by acting through the antiviral effect, or by suppression of augmented cytokine release may reduce the severity of immune-mediated multiorgan damage, what may be significant especially in COVID-19 patients with central obesity and metabolic syndrome. Taking into account the information derived from our training dataset, referring to the antiviral properties of inhibitors of the SARS 3CLpro and the fact that the protease enzyme is essential for the SARS-CoV-2 virus RNA synthesis and replication, the proposed mechanism of action of zafirlukast would be due to drug-induced disruption of the virus replication cycle. It is noteworthy to point out that the drug has been not only identified as having the best antiviral properties, but it has been consistently ranked as number one by all constituents of our meta-ensemble. The pressumed antiviral properties of zafirlukast are also not new. They have been already described by Donkers et al. [42] and Martinez et al. [43] in the context of its antiviral activity against hepatitis B virus (HBV) and hepatitis delta virus (HDV). Zafirlukast has been indicated as one of the most potent inhibitors of human sodium taurocholate *co*-transporting polypeptide (NTCP), the entry receptor for HBV and HDV [42]. The drug was also found to act as an inhibitor of the West Nile Virus (WNV) NS2B-NS3 protease, which is essential for WNV survival and replication in host

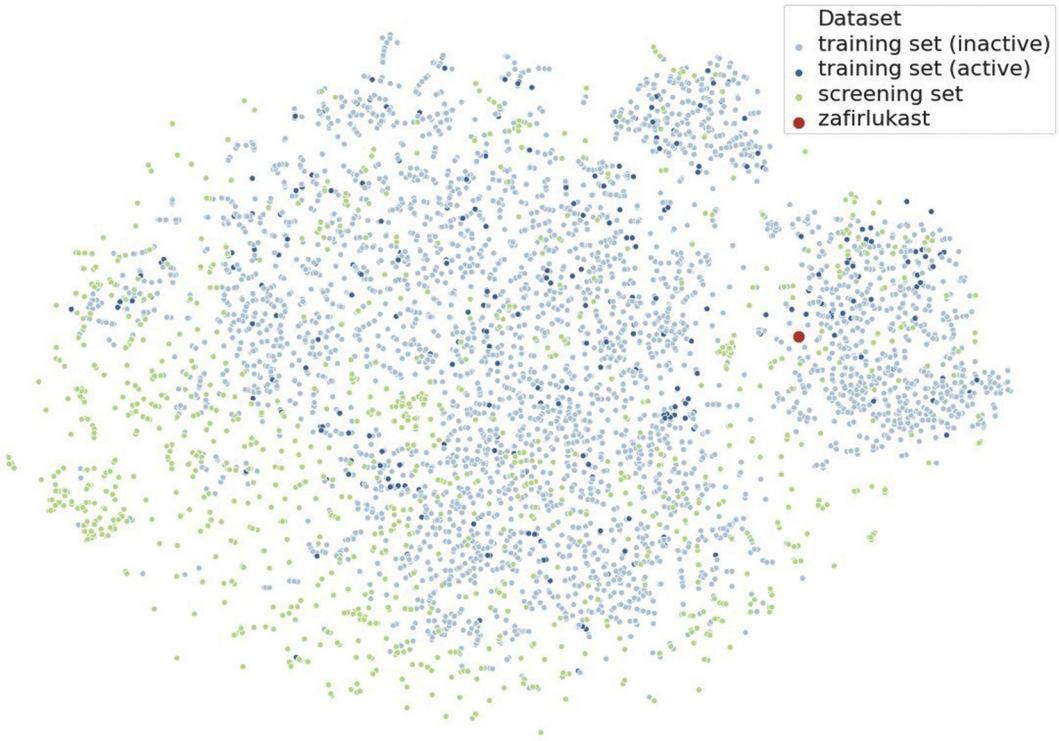

Figure 3. t-Distributed Stochastic Neighbor Embeddings (t-SNE) [37] of a random subsample of inactive molecules from the training dataset (light blue), active molecules from the training dataset (dark blue), all screening molecules from the FDA set of approved drugs (green) and zafirlukast (red dot).

cells [43]. It may be even more interesting, when taking into account the similarity between the cytosolic WNV NS3 and the secretory furin-like serine proteinases of other zoonotic viruses [44].

A remarkable conclusion, which can be drawn from the above mentioned results, is that zafirlukast can be considered as potentially useful against COVID-19 both due to its predicted antiviral properties and its potential to attenuate the cytokine production, and thus to reduce the severe consequences of the disease. Hence, zafirlukast can be seen as a drug combining two distinct mechanisms of action, both crucial for fighting the current pandemic.

Nevertheless, zafirlukast should be perceived rather as an additional preventive therapy against serious organ damage rather that an effective agent in severe COVID-19 symptoms or by reversing already existing lung disfunction. Still, the potential advantage of its use might be effective, when taken as soon as possible after infection. Zafirlukast may be also beneficial due to its safety and convenient administration.

Additionally, we would like to report also on other drugs that can be found among the top 15 rank-ordered repurposing candidates, which, beside zafirlukast, may show antiviral activities. One of them is liothyronine, an active form of thyroxine, which is already under the second phase of two clinical trials (NCT04348513 and EUCTR2020–001623-13-GR) assessing its efficacy and safety for the treatment of critically ill patients with COVID-19 infection [45,46]. We would like to strengthen attention to indomethacin, which is also among the top 15 ranked repurposing candidates. This drug has been already proven to show *in vitro* antiviral properties against SARS-CoV and SARS-CoV-2 [47]. This drug is already under the second and third phases of clinical trial (IRCT20200427047215N1) for determination of its efficacy, safety, and evaluation of the time to clinical recovery in COVID-19 patients with moderate-intensity pneumonia.

Likewise, it may be also worth to mention that among the top 15 repurposing candidates, two sulfonamide derivatives can be identified, namely zafirlukast and metolazone. This observation is interesting, since hybridization of bioactive pharmacophores with sulfonamides has been already used as a strategy to develop sulfonamide antivirals [48]. The sulfonamides build an important pharmacological class, with diuretic, hypoglycemic, antithyroid, anticancer, as well as antibacterial and antiviral activities. Some sulfonamide derivatives have already been reported to show antiviral activity, both *in vitro* and *in vivo*. Amprenavir, an example of HIV protease inhibitors used clinically as well as tipranavir, TMC-126 and TMC-114, contains sulfonamide moieties in their structures. Moreover, nonnucleoside HIV reverse transcriptase, HIV integrase inhibitors, and chemokine antagonists acting as HIV entry inhibitors also possess sulfonamide functionalities in their scaffold [49].

The results based on the manually curated version of the same dataset, after adding the known SARS-CoV-2 3CLpro inhibitors to the training set, show below zafirlukast also the following interesting, high ranked candidates: an example of beta-lactam antibiotic, ampicillin, as well as macrolide antibiotics, erythromycin and clarithromycin. The macrolides are supposed to improve the course of viral infections, at least through indirect mechanisms including anti-inflammatory and/or immunomodulatory effects; however, there is no clear evidence of clinical efficacy of macrolides in coronaviruses infections [50]. Also, a representation of antiviral drugs from the group of inhibitors of DNA polimerases, consisting of valacyclovir, ganciclovir, and its prodrug valganciclovir, was observed. Whereas the results presented in this article provide us with an interesting discovery, in order to carry out more in-depth exploration of the predictive performance and utility of AI-based screenings, the employment of additional and larger datasets would be necessary. Furthermore, exploration of alternative ML techniques, building on alternative molecular representations of the data could lead to further interesting insights. Also, a more in-depth exploration of techniques for effectively tackling the problem of imbalanced data as well additional data enrichments could be an interesting and important area for future research. Moreover, due to dynamically changing pandemic situation, the amount of new evidence on drugs efficacy in COVID-19 is ever growing and dispersed in many unstructured forms such as new research and review articles, reports on clinical trials as well as numerous online platforms. Utilizing these constantly evolving, scattered and unstructured sources of information in combination with AI tools can

constitute an important additional feedback signal for defining the best pharmacotherapy. Finally, important validation aspects involving *in vitro* and *in vivo* experiments as well as clinical trials need to be addressed in the future work to ensure the efficacy and other relevant properties of the proposed drugs.

5. Conclusions

In summary, the AI-based drug discovery screening described in this article identified zafirlukast as the best potential repurposing candidate for COVID-19. This result, put in the perspective of other recent studies in the context of COVID-19, composes an interesting insight, drawing attention to the properties of leukotriene receptor antagonists as a potential treatment against this disease. A notable characteristic of zafirlukast, which can be formulated as a conclusion, is that it could be considered as a potent agent against COVID-19 both due to its predicted antiviral properties as well as its ability to attenuate the so called *cytokine storm*. Thus, these two critical mechanisms of action may be combined in one drug as a novel and promising pharmacotherapy in the current pandemic.

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CRediT author statement

Marcin Delijewski: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review and editing.

Jacek Haneczok: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review and editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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References

[1] World Health Organization. Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update. World Health Organization Weekly Epidemiological Update and Weekly Operational Update; 2020https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[2] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395:470–3.
[3] Wrapp D, De Vlieger D, Corbett KS, Torres GM, Wang N, Van Breedam W, et al. Structural basis for potent neutralization of betacoronaviruses by single-domain camelid antibodies. Cell. 2020;181(5):1004–15.
[4] Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18:463–77.
[5] Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20:273–86.
[6] Vernon JA, Golec JH, DiMasi JA. Drug development costs when financial risk is measured using the Fama–french three-factor model. Health Econ. 2010;19:1002–5.
[7] Zumla C, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-ncov: host-directed therapies should be an option. Lancet. 2020;395:e35–6.
[8] Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. Lancet Digit Health. 2020;2(12):e667–76.
[9] Ke YY, Peng TT, Yeh TK, Huang WZ, Chang SE, Wu SH, et al. Artificial intelligence approach fighting COVID-19 with repurposing drugs. Biom J. 2020;43:355–62.
[10] Gao K, Nguyen DD, Chen J, Wang R, Wei GW. Repositioning of 8565 existing drugs for COVID-19. J Phys Chem Lett. 2020;11:5373–82.
[11] Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. Comput Struct Biotechnol J. 2020;18:784–90.
[12] Levin JM, Oprea TI, Davidovich S, Clozel T, Overington JP, Vanhaelen Q, et al. Artificial intelligence, drug repurposing and peer review. Nat Biotechnol. 2020;38:1127–31.
[13] Zhang H, Saravanan KM, Yang Y, Hossain MT, Li J, Ren X, et al. Deep learning based drug screening for novel coronavirus 2019-nCov. Interdiscip Sci. 2020;12:368–76.
[14] Mohanty S, Rashid M Harun Ai, Mridul M, Mohanty C, Swayamsiddha S. Application of Artificial Intelligence in COVID-19 drug repurposing. Diabetes Metab Syndr. 2020;14:1027–31.
[15] Kandeel M, Al-Nazawi M. Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci. 2020;251:117627.
[16] Parvathaneni V, Gupta V. Utilizing drug repurposing against COVID-19–efficacy, limitations, and challenges. Life Sci. 2020;259:118275.
[17] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ace2 and tmprss2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–80.
[18] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
[19] Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265–9.
[20] Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63:457–60.
[21] Rossi GA, Sacco O, Mancino E, Cristiani L, Midulla F. Differences and similarities between sars-cov and SARS-CoV-2: spike receptor-binding domain recognition and host cell infection with support of cellular serine proteases. Infection. 2020:1–5.
[22] Kowalewski J, Ray A. Predicting novel drugs for SARS-CoV-2 using machine learning from a> 10 million chemical space. Heliyon. 2020;6:e04639.
[23] Sanghai N, Tranmer GK. Taming the cytokine storm: repurposing montelukast for the attenuation and prophylaxis of severe COVID-19 symptoms. Drug Discov Today. 2020;25(12):2076–9.
[24] Almerie MQ, Kerrigan DD. The association between obesity and poor outcome after COVID-19 indicates a potential therapeutic role for montelukast. Med Hypotheses. 2020;143:109883.
[25] National Center for Biotechnology Information. Pubchem bioassay record for aid 1706. The Scripps Research Institute Molecular Screening Center; 2020https://pubchem.ncbi.nlm.nih.gov/bioassay/1706.
[26] Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, et al. Structure of m pro from SARS-CoV-2 and discovery of its inhibitors. Nature. 2020:1–5.
[27] Mahdi M, Mótyán JA, Szojka ZI, Golda M, Miczi M, Tőzsér J. Analysis of the efficacy of hiv protease inhibitors against SARS-CoV-2 s main protease. Virol J. 2020;17:1–8.
[28] Tripathi PK, Upadhyay S, Singh M, Raghavendhar S, Bhardwaj M, Sharma P, et al. Screening and evaluation of approved drugs as inhibitors of main protease of SARS-CoV-2. Int J Biol Macromol. 2020;164:2622–31.
[29] Abian O, Ortega-Alarcon D, Jimenez-Alesanco A, Ceballos-Laita L, Vega S, Reyburn HT, et al. Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. Int J Biol Macromol. 2020;164:1693–703.
[30] Sterling T, Irwin JJ. Zinc 15–ligand discovery for everyone. J Chem Inf Model. 2015;55:2324–37.
[31] Kinch MS, Haynesworth A, Kinch SL, Hoyer D. An overview of FDA-approved new molecular entities: 1827–2013. Drug Discov Today. 2014;19:1033–9.
[32] Yang K, Swanson K, Jin W, Coley C, Eiden P, Gao H, et al. Analyzing learned molecular representations for property prediction. J Chem Inf Model. 2019;59:3370–88.
[33] Landrum G, et al. RDKit: Open-source cheminformatics. https://rdkit.org; 2006.
[34] Chen T, Guestrin C. Xgboost: A scalable tree boosting system. Proceedings of the 22nd ACM SIGKDD international conference on knowledge discovery and data mining; 2016. p. 785–94.
[35] Lematre G, Nogueira F, Aridas CK. Imbalanced-learn: a python toolbox to tackle the curse of imbalanced datasets in machine learning. J Mach Learn Res. 2017;18:559–63.
[36] Wu Z, Ramsundar B, Feinberg EN, Gomes J, Geniesse C, Pappu AS, et al. Moleculenet: a benchmark for molecular machine learning. Chem Sci. 2018;9:513–30.
[37] Maaten LVD, Hinton G. Visualizing data using t-sne. J Mach Learn Res. 2008;9:2579–605.
[38] Funk CD, Ardakani A. A novel strategy to mitigate the Hyperinflammatory response to COVID-19 by targeting leukotrienes. Front Pharmacol. 2020;11:1214.
[39] Twaites BR, Wilton LV, Shakir SA. Safety of zafirlukast. Drug Saf. 2007;30:419–29.
[40] Miller SC, Huang R, Sakamuru S, Shukla SJ, Attene-Ramos MS, Shinn P, et al. Identification of known drugs that act as inhibitors of NF-kappaB signaling and their mechanism of action. Biochem Pharmacol. 2010;79:1272–80.
[41] Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020;10:766–88.
[42] Donkers JM, Zehnder B, van Westen GJ, Kwakkenbos MJ, IJzerman AP, Elferink RPO, et al. Reduced hepatitis b and d viral entry using clinically applied drugs as novel inhibitors of the bile acid transporter ntcp. Sci Rep. 2017;7:1–13.
[43] Martinez AA, Espinosa BA, Adamek RN, Thomas BA, Chau J, Gonzalez E, et al. Breathing new life into West Nile virus therapeutics; discovery and study of zafirlukast as an NS2B-NS3 protease inhibitor. Eur J Med Chem. 2018;157:1202–13.
[44] Seidah NG. Unexpected similarity between the cytosolic West Nile virus NS3 and the secretory furin-like serine proteinases. Biochem J. 2006;393:1–3.

[45] Pantos C, Tseti I, Mourouzis I. Use of triiodothyronine to treat critically ill COVID-19 patients: a new clinical trial. Crit Care. 2020;24:1–2.
[46] Pantos C, Kostopanagiotou G, Armaganidis A, Trikas A, Tseti I, Mourouzis I. Triiodothyronine for the treatment of critically ill patients with COVID-19 infection: a structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21:1–3.
[47] Gomeni R, Xu T, Gao X, Bressolle-Gomeni F. Model based approach for estimating the dosage regimen of indomethacin a potential antiviral treatment of patients infected with SARS COV-2. J Pharmacokinet Pharmacodyn. 2020:1.
[48] Dash RN, Moharana AK, Subudhi BB. Sulfonamides: antiviral strategy for neglected tropical disease virus. Curr Organ Chem. 2020;24:1018–41.
[49] Supuran CT, Innocenti A, Mastrolorenzo A, Scozzafava A. Antiviral sulfonamide derivatives. Mini Rev Med Chem. 2004;4:189–200.
[50] Poddighe D, Aljofan M. Clinical evidences on the antiviral properties of macrolide antibiotics in the COVID-19 era and beyond. Antivir Chem Chemother. 2020; 28:2040206620961712.