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ORIGINAL RESEARCH

Chemoinformatic Analysis of Psychotropic and Antihistaminic Drugs in the Light of Experimental Anti-SARS-CoV-2 Activities

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Introduction: There is an urgent need to identify therapies that prevent SARS-CoV-2 infection and improve the outcome of COVID-19 patients.

Objective: Based upon clinical observations, we proposed that some psychotropic and antihistaminic drugs could protect psychiatric patients from SARS-CoV-2 infection. This observation is investigated in the light of experimental in vitro data on SARS-CoV-2.

Methods: SARS-CoV-2 high-throughput screening results are available at the NCATS COVID-19 portal. We investigated the in vitro anti-viral activity of many psychotropic and antihistaminic drugs using chemoinformatics approaches.

Results and Discussion: We analyze our clinical observations in the light of SARS-CoV-2 experimental screening results and propose that several cationic amphiphilic psychotropic and antihistaminic drugs could protect people from SARS-CoV-2 infection; some of these molecules have very limited adverse effects and could be used as prophylactic drugs. Other cationic amphiphilic drugs used in other disease areas are also highlighted. Recent analyses of patient electronic health records reported by several research groups indicate that some of these molecules could be of interest at different stages of the disease progression. In addition, recently reported drug combination studies further suggest that it might be valuable to associate several cationic amphiphilic drugs. Taken together, these observations underline the need for clinical trials to fully evaluate the potentials of these molecules, some fitting in the so-called category of broad-spectrum antiviral agents. Repositioning orally available drugs that have moderate side effects and should act on molecular mechanisms less prone to drug resistance would indeed be of utmost importance to deal with COVID-19.

Keywords: chemoinformatics, COVID-19, high-throughput screening, phenothiazine, prophylaxis, antihistamine, drug repurposing

Introduction

The rapid pandemic spread of SARS-CoV-2 virus and the resulting COVID-19 has caused havoc worldwide (with millions of deaths, https://www.worldometers.info/coronavirus/) and continue to do so with transmission rate spikes. Hence, there is an urgent need to identify potential pharmacological prophylactic/therapeutic interventions both to prevent SARS-CoV-2 infection and to improve the clinical outcome of COVID-19 patients. At present, only vaccines offer hope but small molecules interfering with SARS-CoV-2 infection would have an added value and could be cost-effective. The shortest path to discover such compounds is via drug repurposing approaches but it should be mentioned, as reported by Edwards,[1] that drug

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repurposing seldom works in humans if there are no clinical observations as background rationale and/or in the absence of a reasonable mechanistic hypothesis. Early 2020, we hypothesized, based upon clinical observations made in several hospitals including the large psychiatric department of the Henri Mondor hospital, Créteil (Paris area), France, and confirmed in several other hospitals, that therapeutic molecules used in the treatment of psychiatric patients might have protected them from SARS-CoV-2 infection and hence explained the paucity of admission to specialized COVID–19 units.[2–5] In order to gain knowledge about the putative molecules that could be repositioned against SARS-CoV-2, we collected a list of 18 compounds most commonly prescribed in the in- and out-patient Henri Mondor treatment programs (Alimemazine, Amisulpride, Aripiprazole, Cetirizine, Citalopram, Clozapine, Cyamemazine, Diazepam, Escitalopram, Hydroxyzine, Lithium, Lorazepam, Melatonin, Nicotine, Quetiapine, Sertraline, Valproate, and Zopiclone). Some of these compounds belong to the phenothiazine class (eg, Alimemazine and Cyamemazine), others contain a benzodiazepine core (eg, Lorazepam) or else are antihistamine drugs with, for example, a core piperazine group (eg, Cetirizine and Hydroxyzine). We investigated further these 18 drugs using chemoinformatic strategies and via literature mining as it is well documented that some molecules from these classes possess in vitro antiviral activities (reviewed in[6,7]). Indeed, 10 out of our 18 drugs have been reported to have in vitro antiviral activities against various types of viruses including HIV, Ebola, HSV, MERS or SARS. Four were chemically close to molecules that display such in vitro antiviral activity and were therefore predicted to also possess such property based on "principle of similarity" commonly applied in medicinal chemistry.[8] While the psychotropic and antihistamine drugs that we were investigating belong to several chemical families, we observed a common trend among these molecules. Eleven (60%) out of these 18 most prescribed compounds were cationic amphiphilic drugs (CADs). CADs are molecules characterized by the presence of a hydrophobic-aromatic ring system and a side chain that carries one (or more) ionizable amine functional group(s) (ie, a basic moiety). Many such compounds accumulate in lysosomes or in other acidic subcellular compartments (ie, lysosomotropic agents,[9] well-known molecules acting on SARS-CoV-2 in vitro via this mechanism are the antimalarial drugs, chloroquine and hydroxychloroquine although the compounds have also many other actions[10–13]). Many CADs are therefore known to interfere with intracellular trafficking (eg, endosomal entry route, clathrin-mediated or not) and several such molecules have indeed in vitro antiviral activity.[7,14] CADs compounds are also known to induce phospholipidosis in vitro (a lysosomal storage disorder), and 14 out of our list of 18 drugs were known or predicted to induce phospholipidosis.[15] These molecules are associated with intracellular traffic perturbations and could play a role in SARS-CoV-2 infectivity.[16] The perturbation of lysosomal function seems to confer anticancer activity to several CAD psychotropic drugs.[17]

From these observations, presumably, many of our 18 molecules could play a role in the early phases of the virus life cycle. In short, in early 2020, our hypothesis was that interesting compounds to reposition against SARS-CoV-2 would be CAD psychotropic and antihistaminic molecules (ie, the ones present in our list of 18 compounds or analogs that possess similar physicochemical properties and chemical substructures). These drugs could perturb virus entry, for instance by interfering with normal endocytosis but could also inhibit directly or indirectly the interaction between the viral Spike protein and the host ACE2 receptor (details about cell entry mechanisms are reported here[18]). These drugs obviously bind to their primary targets (for example, histamine receptors, dopamine receptors, GABA(A) receptor), although the impact of such interactions on COVID-19 is not clear. In addition, it is well known that drugs can interact with several targets and as such, the CAD psychotropic and antihistaminic molecules are likely to also bind to known (eg, the Sigma receptors[19]) and unknown off-targets and act on the virus and/or on the host defense mechanisms. The conclusion of our first analysis was that CAD psychotropic and antihistaminic molecules could confer protection against SARS-CoV-2 infection in psychiatric patients as these subjects receive as treatment a "CAD cocktail" that certainly interferes with the endo-lysosomal viral machinery essential for cell entry, replication and spread to other cells[2] while some compounds (eg, antihistamine drugs) could also down-regulate prominent inflammatory messengers.[14,20] Yet, in our first report, we also mentioned that while such drugs might protect against SARS-CoV-2 infection, many of them do have concerns (eg, toxic side effects if unmonitored) and hence cannot be recommended for mass population prophylaxis and/or treatment in the urgent fight against COVID-19.

When we reported our study about the possible protective potentials of psychotropic and antihistamine drugs

against SARS-CoV-2 infection,[2] in vitro data on SARS-CoV-2 were not available. Since then, low-throughput and high-throughput screening experiments have been performed (see a recent review[21]). To the best of our knowledge, the largest high-throughput screening data open to the research/medical community are available at the NCATS COVID-19 portal (https://opendata.ncats.nih.gov/covid19).[22] These data involve the screening of over 10,000 chemical compounds. We here investigate our initial observations in the light of these new experimental data. We thus further rationalize the potential protective effect of some psychotropic and antihistamine drugs against SARS-CoV-2 infection and propose some already approved drugs (with manageable/tolerable adverse effects) that could be repositioned to protect the general population against COVID-19.

Methods

Data Preparation and Analysis

The first step involved the curation and preparation of the experimental screening data. We downloaded the data on SARS-CoV-2 cytopathic effect (CPE) from the NCATS COVID-19 portal. This assay measures the ability of a compound to reverse the cytopathic effect induced by the virus in Vero E6 host cells (one of the most commonly used cell lines for studying this family of virus). The assay provides valuable basic information about the ability of a compound to restore the cells' function but does not provide indication of the possible mechanism of action(s) of the small chemical compound under study. We also explored using the same Vero E6 cells the cytotoxic effect of these molecules in a counterscreen since the observed effect of some compounds may be mediated through cell viability and could lead to erroneous interpretation of the CPE results. Such information on cell viability is evidently important in the applicability of such compounds in clinical pharmacological interventions. Some additional data are important to take into account in the present analysis and involve the effect of the chemical compounds on human fibroblasts. This assay measures the host cell ATP content as a readout for cytotoxicity. When available, we annotated further the CPE data with the results of this assay. To be able to quickly repurpose a compound, we focused essentially on molecules that have been approved or are in clinical trials (in some instances, drugs are only approved for veterinary use). We thus cross-linked the CPE sample ID numbers to drug names (eg, international nonproprietary names), PubChem SID or CID numbers[23] or to ChEMBL ID numbers[24] and to molecules that possess ATC (Anatomical Therapeutic Chemical Classification system) codes and/or have documented therapeutic indications as found in DrugBank,[25] DrugCentral[26] and eDrug3d.[27] Molecules that are at the preclinical stage (eg, chemical probes) were essentially excluded via this procedure. Additionally, the salts, when present in the chemical file, were deleted using the Maya chemistry toolkit,[28] and the chemistry of the molecules was standardized using our FAF-Drugs4 web server.[29] The drugs in duplicate were removed. Further curation of the CPE data also involved the following: i) removal of a few molecules without potency values (AC50 values are reported for this dataset, ie, concentration for half-maximal activity[30]), ii) investigation of the curve class (ie, the evaluation of the quality of the dose–response curve and thus the quality of the measurements) in the CPE data (a curve class of type 4 is a flat curve indicating no activity) and maximum response (ie, maximum response value detected in the experiment). In such assay, compounds are usually considered active when the maximum response (absolute) value is above 30.[31] Further, we removed molecules that were found highly cytotoxic in the Vero E6 counterscreen assay. From the initial CPE data containing 10,721 assessed samples (some molecules have been screened several times and most are chemical probes), we ended up with a list of 198 bioactive drugs. In this list of drugs, 93 were not tested for toxicity on human fibroblast and for the remaining 105 molecules, only one was found cytotoxic (Disulfiram, used for alcohol addiction, this molecule was also removed not only because of its cytotoxic nature in these assays but also as found to be a promiscuous SARS-CoV–2 main protease inhibitor[32]). At this stage of the analysis, we decided to retain all the compounds including those not annotated for human fibroblast toxicity. We then focused our attention on families of molecules that contain several members and removed some molecules with highly specific disease indication such as Deferasirox (an oral iron chelator given to patients receiving long-term blood transfusions). In this last step of data curation, we grouped the 198 compounds according to chemistry and disease indications and removed molecules that did not fulfill our selection criteria. This step led to the selection of a final list of 161 molecules reported in Table 1. Numerous approaches can be used to investigate low molecular weight chemical compounds in silico (eg,[33–35]) and here we decided to analyze these molecules

Table 1 Investigated Chemical Probes and Approved Drugs

Name	Indication	AC50 (uM)	Fibroblast-Toxicity	ClinicalTrials.gov (Feb 24, 2021)	cLogP	Simple Rule-Based Estimation of Basic Nitrogen Atoms
Abemaciclib	Cancer	1.412537545	Not determined (ND)	No	4.1154	4
Acetopromazine	Psychotropic	12.58925412	No (N)	No	3.8721	1
Acolbifene	Cancer	11.22018454	ND	No	4.9846	1
Amiodarone	Cardiovascular	8.912509381	N	Yes	6.2801	1
Amitriptyline	Psychotropic	12.58925412	N	No	4.4056	1
Amlodipine	Cardiovascular	12.58925412	ND	Yes	2.071	1
Amodiaquine	Infectious	1.584893193	ND	Yes	4.2018	2
Amoxapine	Psychotropic	8.912509381	N	No	3.3035	2
Andrographolide	Infectious	11.22018454	ND	No	1.883	0
Anidulafungin	Infectious	5.623413252	ND	No	−0.4951	0
Apilimod	Infectious	12.58925412	ND	Yes	5.1942	2
Aprindine	Cardiovascular	8.912509381	N	No	4.5009	1
Arbidol (or Umifenovir)	Infectious	8.912509381	ND	Yes	4.1689	1
Aripiprazole	Psychotropic	12.58925412	N	No	4.4351	1
Asenapine	Psychotropic	10	ND	No	4.9405	1
Ataciguat (experimental)	Cardiovascular	12.58925412	ND	No	1.8036	0
Azelastine	Antihistamine	11.22018454	N	No	4.3744	1
Azithromycin	Infectious	11.22018454	N	Yes	1.6569	2
Bazedoxifene	Bone problems and possibly Cancer	3.981071706	N	No	5.6968	1
Benazepril	Cardiovascular	10	N	Yes	0.8715	1
Bencyclane	Cardiovascular	12.58925412	N	No	3.8639	1
Bepridil	Cardiovascular	8.912509381	N	No	4.4044	1
Berbamine (experimental)	Cancer	1.412537545	ND	No	6.2253	2
Berzosertib (experimental)	Cancer	2.238721139	ND	No	1.669	1
Bexarotene	Cancer	12.58925412	N	No	4.799	0
Bifemelane (approved Japan)	Psychotropic	12.58925412	N	No	3.7476	1
Blonanserin (Japan)	Psychotropic	5.623413252	N	No	5.3682	2
Brexpiprazole	Psychotropic	11.22018454	ND	No	3.8983	1
Bromodiphenhydramine	Antihistamine	12.58925412	N	No	3.631	1
Buclizine	Antihistamine	12.58925412	N	No	6.6827	2
Calpeptin (experimental)	Cancer	0.316227766	ND	No	2.8358	0
Carvedilol	Cardiovascular	11.22018454	ND	Yes	3.1668	1
Cenicriviroc	Infectious	8.912509381	ND	Yes	7.2606	1
Ceritinib	Cancer	10	ND	No	5.5817	3
Chlorcyclizine	Antihistamine	12.58925412	N	No	3.6827	2
Chloroquine	Infectious	3.981071706	N	Yes	4.0091	2
Chloroxine	Infectious	12.58925412	N	No	2.8419	0
Chlorpromazine	Psychotropic	8.912509381	N	Yes	4.6069	1
Chlorprothixene	Psychotropic	3.548133892	N	No	5.1216	1
Ciclopirox	Infectious	5.011872336	N	No	1.4285	0
Cilnidipine	Cardiovascular	11.22018454	N	No	3.6409	0
Clemastine	Antihistamine	11.22018454	N	No	4.5988	1
Clioquinol (withdrawn)	Infectious	10	N	No	2.673	0
Clofazimine	Infectious	6.309573445	ND	Yes	6.2781	1
Clomipramine	Psychotropic	7.943282347	N	No	4.4969	1
Closantel (veterinary drug, likely toxic in humans)	Infectious	11.22018454	N	No	6.4242	0

(*Continued*)

Table 1 (Continued).

Name	Indication	AC50 (uM)	Fibroblast-Toxicity	ClinicalTrials.gov (Feb 24, 2021)	cLogP	Simple Rule-Based Estimation of Basic Nitrogen Atoms
Clozapine	Psychotropic	12.58925412	N	No	3.2447	2
Cyclobenzaprine	Initially used as Psychotropic	10	N	No	4.3534	1
Cyproheptadine	Antihistamine	3.981071706	N	No	4.5999	1
Cysmethynil (experimental)	Cancer	10	ND	No	5.9027	0
Dabrafenib	Cancer	12.58925412	ND	No	3.666	0
Danazol	Cancer and endometriosis	12.58925412	N	No	3.4638	0
Dapoxetine	Initially psychotropic agent but now premature ejaculation	12.58925412	N	No	4.2367	1
Deserpidine	Cardiovascular	12.58925412	ND	No	3.6454	1
Desipramine	Psychotropic	8.912509381	N	No	3.6244	1
Desloratadine	Antihistamine	11.22018454	N	No	4.0583	1
Desmethylclozapine (metabolite of clozapine)	Psychotropic	8.912509381	ND	No	2.9918	2
Dexanabinol (experimental)	Cancer	10	ND	No	6.9355	0
Difeterol	Antihistamine	12.58925412	N	No	4.0432	1
Doramectin (veterinary drug)	Infectious	12.58925412	ND	No	5.3516	0
Dosulepin	Psychotropic	12.58925412	ND	No	3.8201	1
Doxazosin	Cancer and hypertension	12.58925412	N	Yes	2.1379	2
Duloxetine	Psychotropic	8.912509381	N	No	3.8368	1
Efavirenz	Infectious	10	N	No	3.6614	0
Emodepside (veterinary drug)	Infectious	7.079457844	ND	No	5.237	0
Enzastaurin (experimental)	Cancer	12.58925412	N	No	3.1099	1
Flumatinib (experimental)	Cancer	7.943282347	ND	No	3.8397	2
Flunarizine	Antihistamine	11.22018454	N	No	5.4576	2
Fluoxetine	Psychotropic	4.466835922	N	Yes	3.6241	1
Fluphenazine-decanoate	Psychotropic	12.58925412	N	No	8.527	2
Fonazine (Japan and Europe)	Antihistamine	28.18382931	ND	No	3.1244	1
Halofantrine	Infectious	11.22018454	N	No	8.1762	1
Haloperidol	Psychotropic	25.11886432	N	No	4.3049	1
Hesperadin (experimental)	Cancer	12.58925412	ND	No	2.3768	1
Hexachlorophene	Infectious	0.223872114	N	No	6.4201	0
Hexetidine	Infectious	3.548133892	N	No	5.2587	1
Homochlorcyclizine (Japan)	Antihistamine	5.011872336	N	No	4.0247	2
Hycanthone	Infectious	12.58925412	ND	No	3.3212	1
Hydroquinidine	Cardiovascular	12.58925412	ND	No	2.7959	1
Icaritin	Cancer	12.58925412	ND	No	4.1341	0
Iloperidone	Psychotropic	12.58925412	N	No	4.3044	1
Imatinib	Cancer	5.623413252	N	Yes	3.9383	2
Imipramine	Psychotropic	8.912509381	N	No	3.8909	1
Lapatinib	Cancer	10	N	No	4.7281	1
Lemildipine (experimental)	Cardiovascular	12.58925412	N	No	3.3887	0
Lercanidipine	Cardiovascular	11.22018454	N	No	4.7102	1
Letermovir	Infectious	10	ND	No	4.8615	1

(*Continued*)

Table 1 (Continued).

Name	Indication	AC50 (uM)	Fibroblast-Toxicity	ClinicalTrials.gov (Feb 24, 2021)	cLogP	Simple Rule-Based Estimation of Basic Nitrogen Atoms
Lomerizine	Antihistamine (treatment of migraines)	12.58925412	N	No	4.4864	2
Lopinavir	Infectious	12.58925412	N	Yes	4.847	0
Loratadine	Antihistamine	10	N	No	4.9774	0
Loxapine	Psychotropic	10	N	No	3.5564	1
Manassantin-A (experimental)	Cancer	3.16227766	ND	No	5.8318	0
Manidipine	Cardiovascular	8.912509381	N	No	2.6132	2
Maprotiline	Psychotropic	8.912509381	N	No	3.7029	1
Masitinib	Cancer	11.22018454	ND	Yes	4.7573	3
Mefloquine	Infectious	11.22018454	ND	Yes	3.5076	1
Melitracen	Psychotropic	11.22018454	ND	No	4.6647	1
Merimepodib	Infectious	12.58925412	ND	Yes	2.7196	0
Mesoridazine	Psychotropic	10	N	No	4.5579	1
Methdilazine	Antihistamine	7.079457844	ND	No	4.2005	1
Methotrimeprazine	Psychotropic	12.58925412	ND	No	4.1492	1
Momelotinib (experimental)	Cancer	12.58925412	ND	No	2.5062	0
Monatepil (experimental)	Cardiovascular	12.58925412	N	No	4.7269	1
Nafronyl	Psychotropic	12.58925412	ND	No	4.2981	1
Naftopidil	Cancer	12.58925412	N	No	3.42	1
Nicardipine	Cardiovascular	10	N	No	1.5582	1
Niraparib	Cancer	12.58925412	ND	No	2.0619	1
Nirogacestat	Cancer	12.58925412	ND	No	4.3631	3
Nitazoxanide	Infectious	3.16227766	N	Yes	1.6871	0
Nitroxoline	Infectious	12.58925412	ND	No	0.7083	0
Oxatomide	Antihistamine	10	N	No	4.2761	2
Pamelor	Psychotropic	12.58925412	ND	No	4.1391	1
Parthenolide	Cancer	10	ND	No	2.7525	0
Pazopanib	Cancer	12.58925412	ND	No	0.9125	2
Periciazine	Psychotropic	10	ND	No	4.1174	1
Perphenazine	Antihistamine and psychotropic	12.58925412	N	No	4.1649	2
Pipequaline (experimental)	Psychotropic	12.58925412	ND	No	4.9763	1
Piperacetazine (prodrug)	Psychotropic	12.58925412	N	No	4.8021	1
Piroctone (experimental)	Infectious and Cancer	7.943282347	ND	No	2.9044	0
Pizotifen	Psychotropic and antihistamine	10	N	No	4.5187	1
Pluripotin (experimental)	Cancer	12.58925412	ND	No	4.2874	0
Prochlorperazine	Psychotropic	8.912509381	N	No	4.6853	2
Promazine	Psychotropic	10	N	No	4.0009	1
Promethazine	Antihistamine	8.912509381	N	Yes	3.9058	1
Propafenone	Cardiovascular	12.58925412	N	No	3.0837	1
Propionylpromazine (veterinary drug)	Antihistamine and neuroleptic	10	N	No	4.3265	1
Protriptyline	Psychotropic	12.58925412	N	No	3.6848	1
Pyrimethamine	Infectious	4.466835922	ND	No	2.5414	2
Quinidine	Cardiovascular	12.58925412	ND	No	2.6104	1

(*Continued*)

Table 1 (Continued).

Name	Indication	AC50 (uM)	Fibroblast-Toxicity	ClinicalTrials.gov (Feb 24, 2021)	cLogP	Simple Rule-Based Estimation of Basic Nitrogen Atoms
Quizartinib (experimental)	Cancer	2.511886432	ND	No	4.7979	2
Refametinib (experimental)	Cancer	11.22018454	ND	No	1.88	0
Remdesivir	Infectious	7.943282347	ND	Yes	0.3048	0
Rescimetol (Japan)	Cardiovascular	12.58925412	N	No	3.6989	1
Reserpine	Cardiovascular	11.22018454	N	Yes	3.5754	1
Retapamulin	Infectious	12.58925412	ND	No	5.218	1
Sarpogrelate	Cardiovascular	12.58925412	N	No	1.8567	1
Serdemetan (experimental)	Cancer	8.912509381	ND	No	3.7237	1
Siccanin (experimental)	Infectious	12.58925412	ND	No	4.3637	0
Spiclomazine (experimental)	Cancer	12.58925412	ND	No	5.2169	1
Spiperone (Japan)	Psychotropic	7.943282347	N	No	3.0219	1
Spiramycin-II	Infectious	12.58925412	N	No	2.4608	2
Sulfatinib (experimental)	Cancer	12.58925412	ND	No	2.0918	1
Teicoplanin	Infectious	14.12537545	ND	Yes	−3.4194	1
Thioproperazine	Psychotropic	11.22018454	N	No	3.2979	2
Thiothixene	Psychotropic	12.58925412	ND	No	2.937	2
Tilorone	Infectious	10	ND	No	4.0607	2
Timiperone (Japan)	Psychotropic	10	ND	No	3.7407	1
Tioguanine	Cancer	10	ND	No	−0.9683	1
Tipifarnib (experimental)	Cancer	12.58925412	ND	No	4.03	2
Tivantinib (experimental)	Cancer	12.58925412	ND	No	4.1837	0
Tizoxanide	Infectious	3.16227766	ND	Yes	1.3547	0
Triamterene	Cardiovascular	7.079457844	N	Yes	0.6075	2
Trifluomeprazine	Psychotropic	10	ND	No	5.0675	1
Trifluoperazine	Psychotropic	12.58925412	ND	No	4.9276	2
Triflupromazine	Psychotropic	11.22018454	N	No	4.8492	1
Trimeprazine (or Alimemazine)	Psychotropic	8.912509381	N	No	4.2192	1
Trimetrexate	Cancer	10	ND	No	1.9786	2
Trimipramine	Psychotropic	10	N	No	4.1092	1
Vilazodone	Psychotropic	10	ND	No	3.6629	1
Vorapaxar	Cardiovascular	8.912509381	ND	No	4.7865	0
Zotepine	Psychotropic	12.58925412	N	No	4.6741	1

Notes: The names of the 161 selected bioactive molecules are reported in the first column. For each compound, the main indication, the experimental AC50 values (see text), the experimental fibroblast toxicity (ND, not determined, N, No), the computed log P (cLogP), and a simple estimation of the number of basic nitrogen atoms are shown. Also, molecules that are in clinical trials for COVID-19 treatments indicated; Experimental and investigational drugs are all labelled in this Table experimental.

with DataWarrior.[36] In this final list, very few molecules are only chemical probes, like Calpeptin (moderate activity against SARS-CoV-2 main protease M^{pro}). They were kept because they are often used to assess some enzymatic activities. The structural classification of chemical entities was then performed using the ClassyFire application.[37]

Results and Discussion

The 161 molecules found to be active in the CPE assay (after excluding compounds that were found to be highly cytotoxic in Vero E6 cells counterscreen assay) are prescribed as treatments in five major disease areas (Figures 1 and 2). Of course, it is important to note that some of the selected drugs can be given to different types of disease but we still attempted to group them into main/major indications.

Molecules that are in the "Allergies" category (different types of allergies are involved) are here all antihistamine compounds. Some of these molecules also have other properties, such as anti-inflammatory effects. This group of compounds includes for instance Loratadine and Desloratadine (eg, allergic rhinitis), Azelastine (eg, allergic and vasomotor rhinitis and allergic conjunctivitis) and Promethazine (eg, used for allergic reactions, nausea and

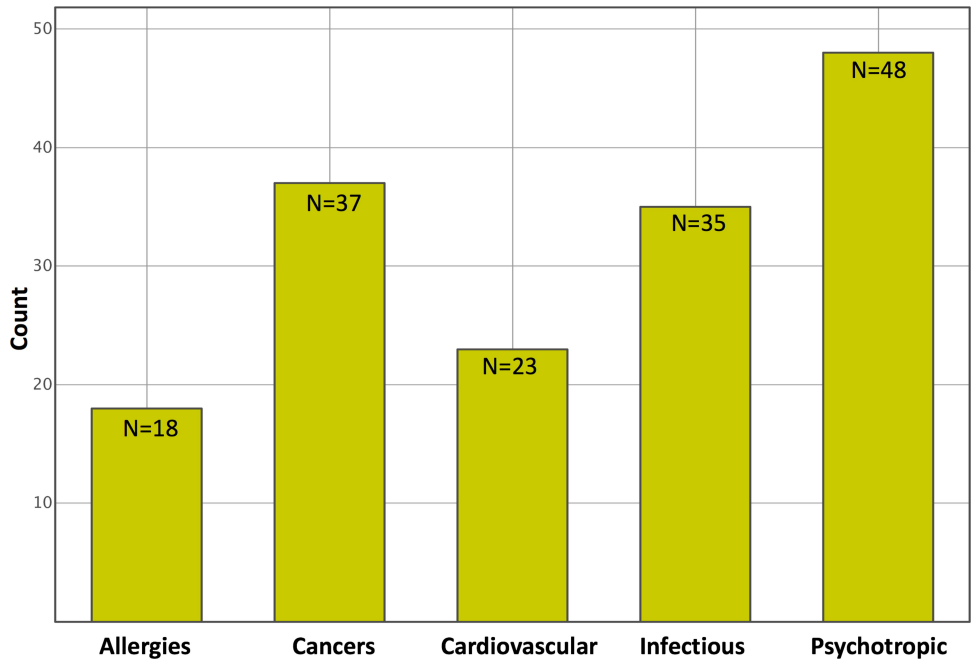

Figure 1 Five major drug indications found to have SARS-CoV-2 cytopathic effect.

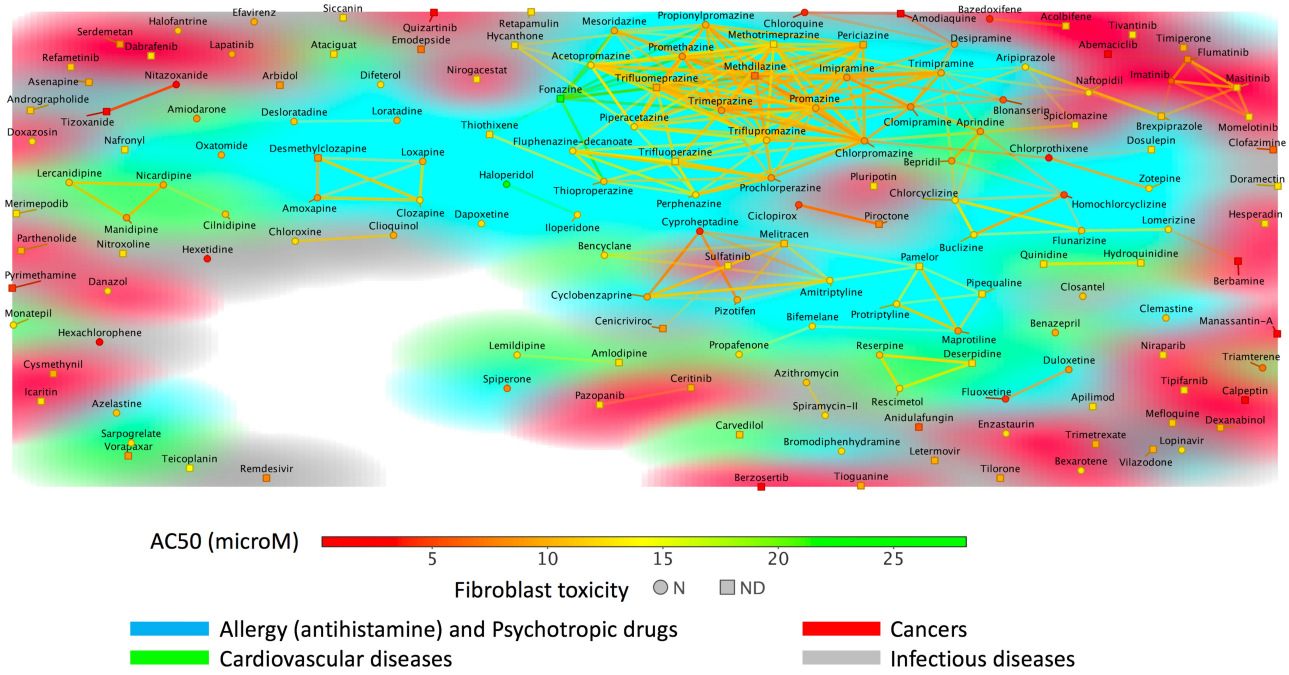

Figure 2 Bioactive compounds (161 molecules) clustered according to the presence of organic functional groups. The molecules that were found to share identical or similar organic functions are connected by lines (eg, the presence of a specific ring system). Increased transparency of the lines reflects decreasing similarity. The compounds are marked either as a circle (molecules not toxic in human fibroblast toxicity assay) or as a square (molecules not tested for such toxicity). The marker symbols and the connecting lines are color coded according to the reported experimental potency values (for this dataset, AC50 values are provided). The background colors behind the markers and lines are color coded according to the disease categories. Yet, as some compounds in the category of "Allergies" are also prescribed in psychiatric settings (indeed some psychotropic drugs were initially used as antihistaminics), we applied the same background color for these two categories to facilitate the reading of this figure. We can observe in this figure a large group of compounds sharing similar substructures (eg, around Promethazine) that have in general moderate activity in these in vitro assays. The figure was generated using DataWarrior version 5.2.1.

vomiting). While not an antihistamine molecule, Colchicine (approved by the FDA for the management of gout) could be present in this group (although it also has indications in Cancers and Cardiovascular diseases). It is an anti-inflammatory drug that could reduce the risk of complications and death from COVID-19 (study of about 4,500 non-hospitalized patients with COVID-19, the odds of death or hospitalization were apparently 21% lower in the group on Colchicine).[38] This molecule is not present in our list of 161 compounds because it was not active in the CPE assays that we investigated and was cytotoxic (ie, indeed this compound can be relatively toxic, depending on the dose). As such, this molecule could possibly act on the exaggerated inflammatory response seen in some patients in more advanced stages of disease progression.

Another group of drugs is anti-cancer agents. Many of these compounds are kinase inhibitors, such as Abemaciclib, Pazopanib, Ceritinib, Lapatinib and Imatinib. Imatinib, a potent ABL inhibitor, was found here to have moderate CPE activity. This compound is in a clinical trial for COVID-19 but other authors noted that this molecule had limited activity on SARS-CoV-2 entry/infection in different in vitro assay types.[39] It is also important to note that some kinase inhibitors are used for the treatment of autoimmune disorders and other complex imbalances of the immune system like for instance, Baricitinib. This compound is used for the treatment of rheumatoid arthritis and is in a clinical trial for treating COVID-19 patients. Some authors suggested that it could be beneficial in preventing virus infectivity via perturbation of endocytosis[40] and/or could be important as an inhibitor of targets in critically ill COVID-19 patients.[41] This compound is obviously not present in our list of anti-cancer agents and was not found active in the CPE assay. Yet, such a molecule could be of interest, for instance to act on the cytokine storm. Also, in the cancer field, Pralatrexate was found able to potently inhibit SARS-CoV-2 replication with a stronger inhibitory activity than Remdesivir.[42] It is not present in our list as was found very cytotoxic in the in vitro assays that we analyzed.

Several drugs prescribed in the field of cardiovascular diseases were also found active in the CPE assay. These include Vorapaxar (reduces the incidence of thrombotic cardiovascular events or with peripheral arterial disease, a molecule proposed as potentially interesting for the treatment of COVID-19 patients[43]), Carvedilol (treatment of heart failure, hypertension, a molecule also suggested in the literature as potentially beneficial for COVID-19 patients via several mechanisms of action[44]) or Nicardipine (antihypertensive properties effective in the treatment of angina and coronary spasms). Another very interesting compound is Bepridil, a long-acting calcium-blocking agent with significant anti-anginal activity. This molecule is within a large network of compounds that share structural similarities and is easily identified with simple chemoinformatics visualization approaches (eg, part of the large Promazine-like compounds, see Figure 2). In fact, it is a CAD that can potentially raise the endosomal pH and that was found highly active in vitro and in animal models against different types of viral infection including Ebola.[45] This molecule has now been shown, after docking computations and experimental validations, to be potent against SARS-CoV-2 in vitro.[46] It is active on the virus main protease and most likely acts on endocytosis and, as such, could interfere with the entry of SARS-CoV-2 into mammalian host cells and slow down replication.

The molecules that belong to the "Infectious Disease" category include molecules with widely different types of activities. For instance, Mefloquine and Chloroquine (anti-parasitics for Malaria), Letermovir (for prophylaxis of cytomegalovirus infection), Cenicriviroc (under clinical trials for the treatment of HIV-infection/AIDS), Nitazoxanide (broad-spectrum anti-infective drug) and Lopinavir (in the treatment of HIV-infection). Several antimalarial drugs (eg, Methylene blue, a cationic dye with a tricyclic phenothiazine-like group (in fact a benzene fused to a thiazine ring), that was used as lead for the development of Chlorpromazine and tricyclic antidepressants, approved by the FDA for many indications including the prevention of urinary tract infections in elderly patients and was used during many years to treat malaria) are known to act in vitro on SARS-CoV-2[47] while the in vitro activity of Cenicriviroc has also been reported.[48] In the present study, however, Methylene blue was not kept in our final list of 161 compounds as the molecule was reported to be cytotoxic in the NCATS COVID-19 results. This molecule is however interesting mechanistically as in vitro it was found to block (low micromolar in a protein-based ELISA setup) the Spike-ACE2 protein-protein.[49] Such a compound is also likely to interact with cell membranes and seems to be a phospholipidosis inducer.[50] Nitazoxanide was, for example, found promising in its ability to hinder the replication of a SARS-CoV-2 isolate[51] and is now in several clinical trials either alone (eg, see[52]), against placebo, or in combination with for instance

Ivermectin (a broad-spectrum anti-parasite medication that was not found to be active in the CPE assays that we investigated here and that was highly cytotoxic in the Vero E6 cell counterscreen, not mentioning potential risks due to interactions or the lack of interactions with some drug transporters in some patients[53]). Another well-known molecule in this category is Azithromycin (an antibiotic medication), which appears to block the binding of the virus to the ACE2 receptor, among others but that was not confirmed as active in various clinical trials, with or without Hydroxychloroquine. It was also found that in 84 elderly patients with suspected COVID-19 treated early with antihistamines (Dexchlorpheniramine, Cetirizine or Loratadine) combined with Azithromycin for the 25 symptomatic cases, could be favorable when monitoring different types of endpoint such as the fatality rate or hospital admission rate.[54] No adverse effects, no hospital admissions and no deaths were reported. Of course, clinical trials would be needed, but this observation is of interest in the context of the present analysis. The synthetic antibacterial drug Clofoctol, suggested to have activity on SARS-CoV-2,[55] is not present in our analysis as not tested in this dataset. A molecule with some similarity, Hexachlorophene, a chlorinated bisphenol antiseptic is present in our list and has some in vitro activity but has also some moderate cytotoxic issues. Hexachlorophene was however inactive when tested for human fibroblast toxicity.

Molecules of the "Psychotropic drugs" category also involve structurally diverse compounds that include, for instance, Clomipramine (an antidepressant, also reported in a very recent study[56]), Chlorpromazine (an antipsychotic that has activity in vitro and is in clinical trial[57–60]), Fluoxetine (an antidepressant, the so-called Prozac),[61] and Haloperidol (an antipsychotic).

Following the above analysis, we then clustered the small molecules based on their chemical structures. Many different approaches can be used for this purpose[62] but as the bioactive compounds investigated here tend to belong to a limited number of chemical classes, a possible way is to group the compounds based on the presence of identical/similar organic functional groups. We investigated our list of 161 molecules using this strategy with the DataWarrior application. The results are shown in Figure 2. As can be seen, a large cluster involves drugs used for allergies and for mental disorders. These molecules all share a phenothiazine group with different types of side chains (molecules around Trimeprazine also named Alimemazine or around Promazine or Fluphenazine, a piperazine ring phenothiazine). Other molecules that are chemically closely related involve for instance Clomipramine or Imipramine. Here, the phenothiazine group is not present but a dibenzazepine group is found instead. With such a simple data visualization method, it becomes possible in one single figure to highlight molecules that could be of interest, along this line, the case of the cardiovascular Bepridil drug mentioned above is of interest.

Earlier we suggested that cationic amphiphilic psychotropic and antihistamine drugs might play a significant protective role as witnessed by the relatively low representation of the psychiatric patients among the COVID-19 clinical units.[2] The notion of CADs and/or lysosomotropic active agents is not clearly defined but in general, the scientific community considers that the cationic character of a molecule can be flagged by the (predicted) value of its highest basic pKa while the amphiphilicity can be estimated by (computed) log P values.[14,50] Such compounds contain organic bases with basic pKa above 6 or 7 and are expected to carry one or more positive charges at physiological pH (even more so in the acidic environment of the endosomal-lysosomal system) while the computed log P value of these molecules is in general above 3. If we apply such criteria to our list of 161 molecules, 125 compounds have a computed log P above 3 and among these, 105 have at least one positive charge, suggesting that about 65% of the compounds could be CADs. Obviously these global physicochemical properties are present in a variety of drugs that act in many therapeutic areas. Here we found such compounds in all the five disease categories reported in Figure 1.

From our analysis, the chemical structures or substructures of some CAD compounds that would seem interesting to interfere with SARS-CoV-2 infection are illustrated in Figure 3. According to the automated structural classification package ClassyFire, the main chemical classes involve molecules that contain, as a core, a phenothiazine group (eg, Promazine), a benzazepine group (eg, Imipramine), a benzodiazepine group (eg, Clozapine), a dibenzocycloheptene group (eg, Cyproheptadine), a benzocycloheptapyridine group (eg, Desloratadine), a diazanaphthalene group (eg, Azelastine) or a benzene and substituted derivative group (eg, Homochlorcyclizine or Buclizine, in this case, a piperazine ring is present in the core region). Of importance, other CAD molecules used in different therapeutic areas could be valuable but as

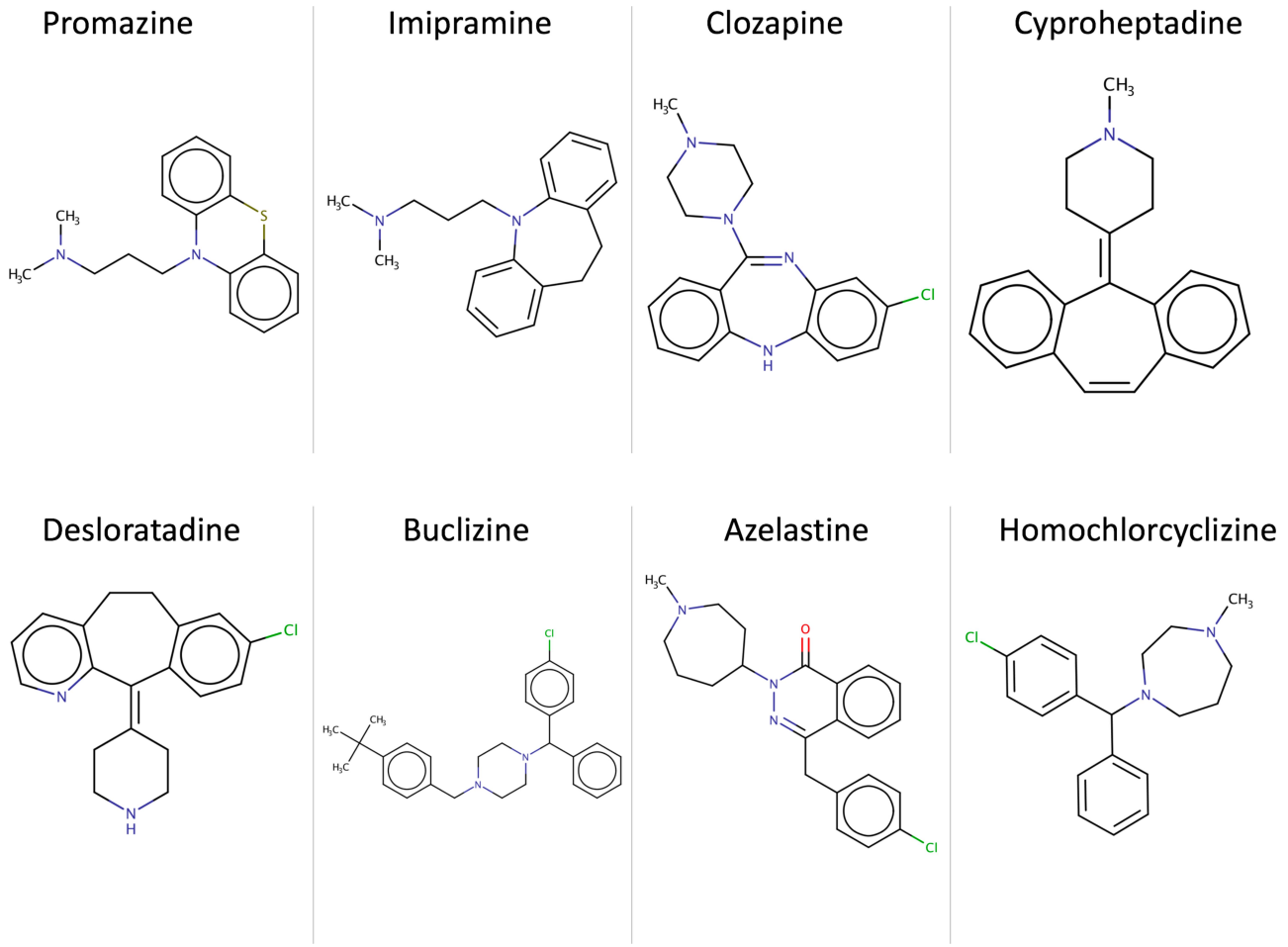

Figure 3 The types of CADs that could interfere with the SARS-CoV-2 life cycle in vitro following our clinical and chemoinformatics analysis. These molecules have a hydrophobic-aromatic ring system and a side chain that carries one (or more) ionizable amine functional group(s). The largest family of molecules contain a phenothiazine group (eg, Promazine, 16 molecules have such a group). The figure was generated using MarvinView from the ChemAxon suite.

compared to cationic amphiphilic psychotropic and antihistamine drugs, we have no clinical observations suggesting a possible protective effect, yet, in vitro studies definitively suggest that these compounds are of interest.

In vitro data can give some insights about the potential of a molecule but cannot predict if a molecule is going to be active in humans. Along the same line, most (small) animal models to study such type of virus tend also to be of limited values to select compounds as they do not reproduce the complexity of the human body.[63] But, interestingly, after mining 219,000 digital health records, Reznikov et al[64] have reported that prior usage of Loratadine, Diphenhydramine, Cetirizine, Hydroxyzine or Azelastine was associated with a reduced incidence of positive SARS-CoV-2 test results in individuals of 61 years and above. Loratadine and Azelastine are present in our list of 161 drugs. Loratadine and Azelastine were also found in other reported experimental screening data available at the open NCATS portal to perturb virus entry via modulation of the ACE2-Spike protein interaction (similar results in this assay were apparently not found for Desloratadine). Diphenhydramine was not tested in the data that we downloaded from the NCATS portal but the highly similar molecule Bromodiphenhydramine was found active in the CPE assay. Yet, Reznikov et al reported that Diphenhydramine was indeed active in vitro. Hydroxyzine and its active metabolite, Cetirizine, were not found active in the CPE assays that we analyzed nor in other assays reported at the open NCATS portal but Hydroxyzine was found to impede the interaction between the viral Spike protein and the human receptor ACE2 and as such could interfere with virus entry (action at the level of the Spike could also be of importance for SARS-CoV-2 virulence). In our hands, Hydroxyzine has only moderate in vitro activity (unpublished data) but we listed it as a very interesting CAD[2] and so other authors.[9] In fact,

clinical observations suggest that Hydroxyzine could reduce mortality in patients hospitalized for COVID-19 most likely due to the anti-inflammatory properties of the compound.[3] These data suggest that additional investigations are needed for this compound to fully understand the molecular mechanisms at play and fully assess its activity on the virus and on the host. Along the same line and with the idea of drug combination, it seems possible that the use of two anti-histamine molecules, Cetirizine and Famotidine (not predicted to be CAD), both found to be inactive in the analyzed CPE assays, might be a safe and effective approach to reduce the severity of COVID-19, presumably via a modulation of the histamine-mediated cytokine storm.[65] Again, one has to be cautious with in vitro data and statistics performed on electronic health records, yet, the data reported above definitively suggest that some of these CAD molecules could be of interest.

Overall, the present analysis, together with other studies,[4,9,66–72] supports our initial observation[2] and suggests that some psychiatric patients could have been protected by their pharmacological treatments. Along this line of reasoning, it should also be mentioned that these patients receive in general a cocktail of drugs (psychotropic and anti-histamine molecules) including several CAD compounds possibly working on different molecular mechanisms. Our analysis also highlights some interesting CADs that act on other types of diseases, such as cardiovascular diseases.

Conclusions

From the above analysis, we suggest that some antihistamine and psychotropic CADs could protect humans from SARS-CoV-2 infection while some of these drugs might be also beneficial at more advanced stages of the disease. Some CAD molecules may only have moderate anti-viral activity at nontoxic concentrations in vitro but could still be of interest (eg, combined with other treatments). The molecular mechanisms involved are likely to be complex, from perturbation of endocytosis, membrane fusion, inhibition of catalytic site and/or of protein–protein interactions to direct binding to some specific membrane receptors. For example, a recent investigation applied surface plasmon resonance to study some antipsychotic drugs and reported that several compounds could bind directly to ACE2 and partially inhibit this virus entry mechanism.[73] It is of course important to note that psychotropic compounds can induce side effects and might not be safe enough to be prescribed for prophylaxis to a population not concerned with psychiatric issues. Yet, with regard to SARS-CoV-2 infection, it would seem possible to replace some psychotropic CADs with antihistamine CADs. For prevention purposes, it should also be mentioned that even molecules with moderate in vitro activity might be relevant, while it is also known that, if needed, most antihistamine CADs could be tolerated at higher doses than usually prescribed without inducing severe side effects. Drug combinations could be beneficial, even more so for drugs that have low to moderate toxicity[74] and usually for compounds that act on different targets and mechanisms. We anticipate many interesting results in this area, for example, the recently demonstrated activity of three drugs (not tested in the dataset investigated here): Clomiphene (selective estrogen receptor modulator and a non-steroidal fertility medicine for women), Vortioxetine (an antidepressant drug), and Asenapine (an atypical antipsychotic drug). All three molecules are, according to our computations, CAD compounds, and in vitro, it seems that the combination is much more potent than each compound used alone.[75] Obviously, further investigations are needed to evaluate the potential additivity, synergy and hopefully not antagonism of the CADs discussed above. Yet, if active in humans, some of these molecules (or a combination of compounds) may help to face the emergence of variants or the rapid decline of neutralizing antibodies.[76–78] We believe that clinical trials are now needed to clarify the type of patients that could benefit from these drugs and at which stage of the infection they should be given, prophylaxis being a potential option. Indeed, many medical practitioners and scientists have urged the authorities to consider some antihistamine agents for clinical trials, at least in France, but so far, nothing has apparently been decided. While vaccines are of very high importance, the many drawbacks (manufacturing capabilities, shipping and storage conditions, public acceptance, time to administrate the drug to billions of people, risks with variants …) call for alternative and/or complementary treatments and preventive approaches in the form of safe, orally available, small molecules that target, if possible, mechanisms not prone to drug resistance.

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Disclosure

The authors declare that they have no conflicts of interest for this work nor any competing financial interests or

personal relationships that could influence the work reported in this paper.

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