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Resources and computational strategies to advance small molecule SARS-CoV-2 discovery: Lessons from the pandemic and preparing for future health crises

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ABSTRACT

There is an urgent need to identify new therapies that prevent SARS-CoV-2 infection and improve the outcome of COVID-19 patients. This pandemic has thus spurred intensive research in most scientific areas and in a short period of time, several vaccines have been developed. But, while the race to find vaccines for COVID-19 has dominated the headlines, other types of therapeutic agents are being developed. In this mini-review, we report several databases and online tools that could assist the discovery of anti-SARS-CoV-2 small chemical compounds and peptides. We then give examples of studies that combined in silico and in vitro screening, either for drug repositioning purposes or to search for novel bioactive compounds. Finally, we question the overall lack of discussion and plan observed in academic research in many countries during this crisis and suggest that there is room for improvement.

Contents

1. Introduction

Since the occurrence of the Coronavirus Disease 2019 (COVID-19), a pathological process mediated by SARS-CoV-2, several millions of deaths worldwide (https://www.worldometers.info/coronavirus/) have been monitored. On top of this situation, we are witnessing a major crisis that is affecting the entire world economy and that is also devastating. SARS-CoV-2 is a coronavirus similar to SAR-CoV-1 (emerged in 2002) and MERS-CoV (emerged in 2012) that infect vertebrates. It is a large, enveloped, single-stranded positive-sense RNA virus [1]. Its genome comprises several open reading frames (ORFs), two-thirds of which encode nonstructural proteins (Nsp) that make up the replicase complex. The remaining encodes nine accessory proteins (ORF) and four structural proteins: Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N), of which the Spike protein mediates entry into host cells via binding to the angiotensin-converting enzyme 2 (ACE2) receptor [2–6]. The Spike, an oligomeric transmembrane protein, can be cleaved and

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further activated by several enzymes [7,8], including the host surface serine protease, TMPRSS2 [3] (Fig. 1). The severity of the host response depends on numerous factors, including an innate response to viral recognition [9,10]. If the antiviral response is delayed or inhibited, viral proliferation can lead to the large-scale recruitment of neutrophils and monocyte-macrophages to the lungs, creating a hyper-inflammatory environment [10]. It has been found, in some COVID-19 patients, that there is an intense release of pro-inflammatory cytokines, i.e., cytokine storm (CS) [11–14], and in some patients, rapid progression to Acute Respiratory Distress Syndrome can occur [15–17].

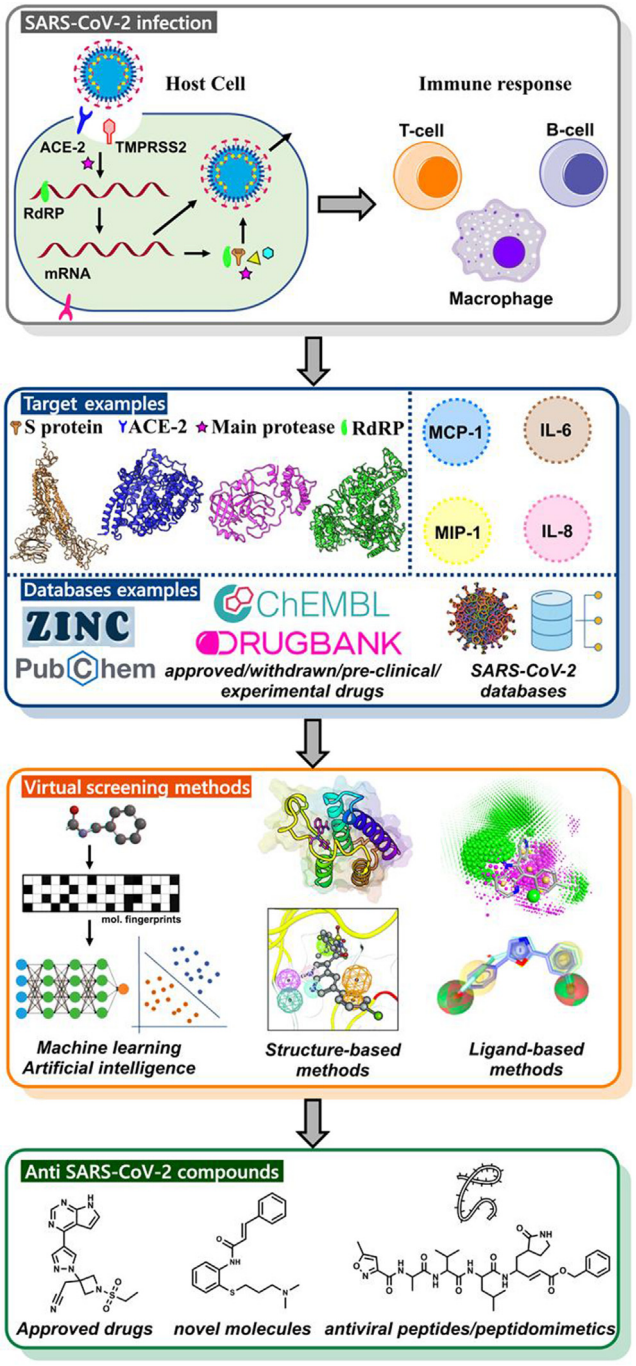

Fig. 1. The virtual screening workflow for the identification and development of COVID-19 treatments using different drug discovery tools. This figure was inspired by the study reported here [215].

Many different strategies can be used to identify disease prevention drugs and/or treatments. In the present context, considering the virus life cycle, one may aim at drugs acting at different stages of the infection (e.g., entry, replication, and dissemination…) [7,18–24]. The drugs could be small chemical compounds and (stapled) peptides [21,25–32], therapeutic proteins including antibodies or nanobodies [33–45], vaccines [46,47] and cells [48–50]. These drugs could interfere with the functioning of viral macromolecules and/or with the host proteins and/or complex not fully understood molecular mechanisms and pathways (e.g., many cationic amphiphilic drugs act on specific targets but also on endocytosis [51–65].

As in all drug discovery project involving small molecules (but also often for other types of therapeutic agents), there are many ways to prioritize targets depending on the goal (hit one target, several targets in a pathway…) [66–74]. Once some targets are selected, experimental high-throughput and in silico screening can be performed. If 3D structures are known or can be predicted by homology modeling [75–77], a critical step for target prioritization usually involves the identification of druggable or ligandable pockets (binding cavities, hot-spots, and cryptic sites) [78–84]. For SARS-CoV-2, major efforts have indeed been made in the field of structural biology (e.g., mainly X-ray and Cryo-EM considering the size of the macromolecules) [85] while homology modeling and related structural bioinformatics servers have in general launched a special service on "Covid-19" (i.e., pages dedicated to SARS-CoV-2 protein prediction and/or analysis). Further, knowledge about the SARS-CoV-2/human interactome is critical to assist the selection of targets and/or the discovery of drug candidates [86–89]. Comparisons with other viruses can obviously give important insights about the molecular mechanisms at play and about valuable targets [90]. Taken together, about 20 proteins directly linked to the disease and involved at different stages of the SARS-CoV-2 virus life cycle could be druggable, including entry into the host cells (e.g., the viral Spike and the host ACE2 and TMPRSS2 proteins), RNA replication, and transcription (e.g., helicase and RNA-dependent RNA polymerase (RdRp)), and translation and proteolytic processing of viral proteins (e.g., viral main protease (Mpro), 3CLpro and the papain-like (PLpro) protease) (Fig. 1). Clearly, many other host proteins and protein–protein interactions can also be considered (e.g., possibly the CD147-Spike interaction and a few hundred others).

As mentioned above, developing (antiviral) drugs (from small molecules to vaccines) is extremely challenging [91,92] and thus, selecting a strategy is obviously critical (e.g., designing a novel compound, a peptide, targeting the enzymes catalytic sites or exosites including allosteric sites…use approved drugs, virtual compounds, etc.). For example, while it might seem easier to identify small molecules inhibiting the catalytic site of viral enzymes as compared to finding inhibitors of protein–protein interactions, mutations in the viral genome can lead to amino acid changes in catalytic centers and possibly drug resistance, thereby making the compound totally or partially ineffective in a short period of time [93,94]. This situation is less likely at protein–protein interaction (PPI) interfaces [94–97]. Also, covalent binders [98] can be of interest, definitively to act on viral enzymes [99] but also to block PPIs as seen in the field of cancer [100]. Further and obviously, to find drugs, it is necessary to understand as much as possible the molecular mechanisms at play, and thus, important biochemical and biological studies have to be performed with associated efficient in vitro assays and animal models. These might be very difficult for complex diseases in general and definitively for this virus [101,102]. Thus, each drug discovery strategy, each selection of targets or pathways, has strengths and weaknesses (e.g., in infectious diseases it could be interesting to target the host proteins to reduce resistance, in oncology the selection of the right therapeutic agents

has to be consider early in the process if for instance the drug needs to penetrate some tumors, in such a case, some biologics are not appropriate). Along the same line of reasoning, it is well-known that time factor and cost have to be considered. The search for drug candidates can take years (e.g., the design of novel antiviral compounds starting from the screening of a large compound collection with various optimization steps including Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties) while other approaches are in general quicker such as drug repurposing or repositioning (e.g., [103–114]). Vaccine and antibody development can also be a long and difficult process with potential additional problems for microorganisms with moderate and high mutation rates not even mentioning, manufacturing, shipping, and storage problems and overall public acceptance [115,116] when it comes to administration to billions of people. What is also obvious from the above is that to design and find treatments, a large number of skills and methodologies are required. Altogether, to face a pandemic (or a global health) crisis, it would seem, at least in academia and at a national level if easier to implement at first, that all the interested scientists should be involved in the process, and that a roadmap should be collectively decided, avoiding as much as possible silo mentality, silo working and related devastating human behaviors commonly seen during a crisis.

In this mini-review, we are interested in computational methods that can assist the so-called early stages of drug discovery. We will focus on tools dedicated to the identification of low molecular weight drug candidates. First, we will briefly introduce some of the computational/data science approaches that can be used to gain insights to search for drug candidates. This first section will also present several online resources and databases that have been used or developed to study SARS-CoV-2. Readers specifically interested in computational approaches that facilitate the development of vaccines or antibodies can find many recent articles and reviews on the topic (e.g., [92,117–126]. Then, we will give examples of studies that combined in silico and experimental approaches to identify putative chemical probes. Finally, we discuss the way research, essentially in academia, has been organized in several countries and suggest possible avenues for improvement.

2. Virtual screening methods and online resources to assist the study of SARS-CoV-2

In modern days, many different in silico approaches can be used to assist the design of a drug candidate or drug, from data (e.g., text and image) mining (e.g., annotated drug databases, antiviral peptide databases, electronic health patient records…), genome analysis, comparative genomics, multiple sequence alignments, visualization tools for epidemiological studies, analysis of macromolecular interaction networks, structural predictions (e.g., comparative modeling, protein folding…), antibody-drug conjugate, analysis of point mutations, protein docking, various types of molecular simulation engines (e.g., for proteins, peptides, small molecules, cell membrane, DNA, RNA, glycans, and interactions among these molecules…), binding pocket predictions, PROTACs (e.g., degradation of viral protein capsids), transcriptomic profile analysis, virtual screening (from small collections of approved drugs as in drug repositioning or repurposing projects to the screening of ultra-large virtual libraries), hit to lead optimization, drug combination, computational polypharmacology and compound profiling, ADMET prediction, multiparameter optimization methods associated with novel data visualization approaches, systems biology, systems pharmacology, with or without the use of machine learning and artificial intelligence (AI) algorithms depending on the type of methods, available data and the stage of the projects [19,77,80,127–180]. Clearly, at present, some computational approaches are more mature than others and some are not realistic [181–183].

With regard to the search for bioactive anti-SARS-CoV-2 molecules, a starting point could involve gathering information about SARS-CoV-1 and related viruses (e.g., molecular mechanisms, potential targets, structural predictions of SARS-CoV-2 proteins in 3D via homology modeling…) in parallel to the generation of new data, experimental or theoretical [184]. For example, numerous antiviral molecules are known [90] and could be used as starting points to explore the almost infinite chemical space [185]. These molecules act on different targets and on different types of molecular mechanisms. From such knowledge, different types of algorithms can be used, such as virtual screening (VS) approaches. Indeed, these methods are known to play a direct role in drug discovery by enabling the identification/optimization of hit or lead compounds that can exert therapeutic effect by binding to one or more targets (mainly proteins but other macromolecules are also considered, such as RNA and DNA) (e.g., [186,187]). Virtual screening methods allow for the screening of large databases of compounds (e.g., real or virtual small chemical molecules, approved and investigational drugs, short peptides…) [134,141,188–190]. A short list of molecules selected after the VS computations are then validated experimentally, providing insights into the underlying mechanism of action and providing interesting starting points for further developments. The two prominent strategies used for VS are ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS). The main approaches for LBVS are similarity-based (shape or chemical fingerprint) approaches and pharmacophore-based methods [191–194]. Quantitative structure–activity relationship (QSAR, employing various types of machine learning and artificial intelligence algorithms, but these approaches can also be used in docking, binding pocket prediction, scoring…..) methods represent other types of powerful ligand-based techniques [107,127,132,137,138,142,195]. SBVS involves molecular docking of chemical libraries into one or several binding pockets, followed by qualitative and quantitative estimation of the docking poses [141,196]. With such approaches, it is possible to target a catalytic site, an allosteric site, or a pocket present at macromolecular interfaces [80,81,151,197]. The most appropriate pockets can be selected, either for docking or de novo compound generation taking into account properties of the cavity [198–202]. In most cases, flexibility of these putative targets/pockets have to be investigated [147,148,156]. The compound collections can be, like in LBVS studies, approved, investigational or experimental molecules [203], purchasable compounds and virtual compounds [204], covalent binders [130,205] or small fragments [206]. Different types of scoring functions can then be used to select the molecules for experimental assays [155,157,160,207–211]. LBVS and SBVS can be combined if the right data are available [134]. Then, as new knowledge is being reported, various types of data mining approaches and workflows can be developed and used [212]. It becomes possible to, for instance, develop statistical predictive models based on experimental screening data so as to predict the bioactivity of a novel compound [213] while, as the 3D structures of many potential targets are now known, SBVS can be performed on different binding pockets with, for instance, ultra-large compound collections [150].

During the Covid-19 pandemic, in wet and dry laboratories alike, numerous projects were initiated and supported by short-term research grants. In the field of computational and data sciences, a tremendous amount of work has been accomplished (e.g., online tools, open databases) in a short period of time [152]. These developments are of high interest as these approaches can help to design chemical probes, drug candidates, therapeutic peptides or proteins and generate new ideas [214]. Further, if these

tools and databases are properly maintained (thus the question about short-term funding), they should be also essential for future research projects and for teaching purposes. What was also impressive, during this crisis, was the amount of computer power available. Most computer groups could have access to super computers and the difficulties were elsewhere, the lack of funding to employ scientists with a proper training in both, computer/data sciences and drug discovery (small molecules and/or biologics).

We have collected several of these online tools/databases, especially those dedicated to drug design (see Supplement Table 1). Yet, some of these are not directly concerned by drug design per se but can be used to gain knowledge about SARS-CoV-2, from genome analysis, visualization tools for epidemiological studies, approaches to study potential therapeutic targets, or to map variants on the 3D structures of the viral proteins (e.g., in binding pockets, in neutralizing antibody binding regions, to design vaccines that would still be effective against Covid-19 variants. . .). With regard to drug design, the online tools allow to run different types of virtual screening computations (e.g., already synthesized or virtual compounds, drug repositioning, peptide docking). At present, several annotated compound databases are available and can be used to develop predictive statistical models that should facilitate the selection or design of more active molecules. As new tools are reported basically every week, we also implement all the URLs on our website, https://www.vls3d.com/, Shortlist page, and all are flagged by the word "Covid-19" such that users can carry out a simple search using, for instance, the Google Chrome Find utility.

3. In silico and in vitro screening to search for novel anti-SARS-CoV-2 compounds

Many different types of computations have been carried out and combined with experimental approaches to search for anti-SARS-CoV-2 molecules. As thousands of articles have been reported, it is only possible to mention some here. For example, we will not cover the following studies to save space [216–227].

Jin et al. identified a mechanism-based peptidomimetic inhibitor N3 **1** (Fig. 2) using computer-aided drug design (CADD) techniques [228]. They solved the crystal structure of the Mpro of SARS-CoV-2 in complex with this compound. The crystal structure revealed that N3 was covalently bonded to the catalytic cysteine (C145) of Mpro. Eight additional compounds, Ebselen **2**, Disulfiram **3**, Tideglusib **4**, Carmofur **5**, Shikonin **6**, PX-12 **7**, TDZD-8 **8**, and Cinanserin **9** (Fig. 2) were identified through a combination of structure-based virtual and high-throughput screening of over 10,000 compounds, including approved drugs, drug candidates in clinical trials, and other pharmacologically active compounds. Out of eight compounds, **2**–**8** showed half-maximal inhibitory concentrations (IC50) ranging from 0.67 to 21.4 μM, whereas compound **9** (Cinanserin) has an IC50 value of 125 μM for Mpro. One of these compounds (Ebselen) also exhibited promising antiviral activity in cell-based assays. Yet, some of these molecules like Ebselen have to be considered with caution as suggested to be a nonspecific promiscuous protease inhibitor [229].

Dai et al. designed two inhibitors, **10** and **11**, by analyzing the substrate-binding pocket of SARS-CoV Mpro [230]. Both compounds strongly inhibited the activity of Mpro (IC50 values of 0.0 53 ± 0.005 μM and 0.040 ± 0.002 μM for **10** and **11**, respectively) and showed good antiviral activity in cell culture. They also determined the crystal structures of SARS-CoV-2 Mpro in complex with these inhibitors, which revealed that the aldehyde groups of **10** and **11** are covalently attached to C145 of Mpro.

In another study [231], a consensus docking-based virtual screening protocol was applied to ~ 2000 approved drugs to find inhibitors of Mpro of SARS-CoV-2 using Glide SP, AutoDock Vina, and AutoDock 4.2. The predicted poses of the compounds were extensively scrutinized in terms of consensus docking score, intermolecular contacts, conformation, stability in molecular dynamics simulations, and potential for synthetic modification. Seventeen compounds were evaluated for Mpro inhibition, in which 14 compounds showed a reduction of Mpro activity at 100 μM concentration. Among these 14 compounds, five compounds, manidipine **12**, boceprevir **13**, lercanidipine **14**, efonidipine **15,** and bedaquiline **16,** exhibited the IC_{50} values of 4.8, 5.4, 16.2, 38.5, and 18.7 μM, respectively.

Gimeno et al. performed docking-based virtual screening of two different libraries of approved drugs against the Mpro structure using Glide, FRED, and AutoDock Vina [232]. The study led to the identification of Carprofen **17** and Celecoxib **18** as weak noncovalent binders of Mpro, showing 3.97% and 11.90% inhibition at 50 μM concentration, respectively.

White et al. targeted the SARS-CoV2 helicase (Nsp13), which is critical for viral replication and the most conserved nonstructural protein within the coronavirus family [233]. By combining homology modeling and molecular dynamics approaches, they generated structural models of the SARS-CoV2 helicase in its apo- and ATP/RNA-bound conformations. The subsequent high-throughput virtual screening of ~970,000 chemical compounds against the ATP binding site of Nsp13 led to the identification of two drugs, Lumacaftor **19** and Cepharanthine **20**, that displayed significant activity in inhibiting Nsp13 ATPase activity in purified recombinant SARS-CoV-2 helicase with estimated IC_{50} values of 0.3 and 0.4 mM, respectively.

Richardson et al., by applying artificial intelligence algorithms, identified Baricitinib (**21**) as a potential drug for COVID-19 infection [234,235]. Baricitinib is a potent and selective inhibitor of the Janus kinases 1/2 (JAK1/JAK2) and is currently used in the therapy of rheumatoid arthritis. Based on the results of the BenevolentAI's knowledge graph tool, Baricitinib has been proposed to exert anti-cytokine effects as well as it was predicted to alter virus entry by inhibiting AP2-associated kinase 1 (AAK1) and cyclin G-associated kinase (GAK), which are likely involved in SARS-CoV-2 endocytosis. The BenevolentAI's knowledge graphical method utilizes machine learning to integrate the scientific information on the biological processes involved in viral infection with that on the mechanisms of action of available drugs in order to identify potential new therapeutic targets and agents [236]. Stebbing et al. validated the AI-prediction by performing the in vitro pharmacology of Baricitinib across relevant leukocyte subpopulations coupled to its in vivo pharmacokinetics, which revealed that Baricitinib inhibited signaling of cytokines implicated in COVID-19 [237,238]. In addition, the inhibitory effects of baricitinib were also evaluated on human numb-associated kinase (hNAK) members, such as AAK1, BIKE, and GAK, for which it showed affinities in the nanomolar range (8.2 nM, 20 nM, and 120 nM, respectively). The NAK enzymes are believed to facilitate the propagation of coronavirus in epithelial cells [234,239,240]. Baricitinib triggered inhibition of NAKs led to reduced viral infectivity in human primary liver spheroids [235,237]. Besides the use of AI in drug discovery, it was recently applied to improve the diagnosis or early warning signs of COVID-19 infection [241]. For instance, researchers at King's College London, in collaboration with Massachusetts General Hospital, designed the COVID Symptom Tracker, developed an AI-based smartphone app that monitors viral transmission and symptoms [242]. This tool identified the importance of anosmia as an early warning symptom. The AI-powered NHSX contact tracing app warns users about viral exposure and so dramatically reduces transmission rates. Alerts are triggered when users self-report symptoms or test positive while respecting anonymity.

Wu et al. used the fact that the Spike protein of SARS-CoV-2 contains a furin cleavage site and proposed that furin could be a

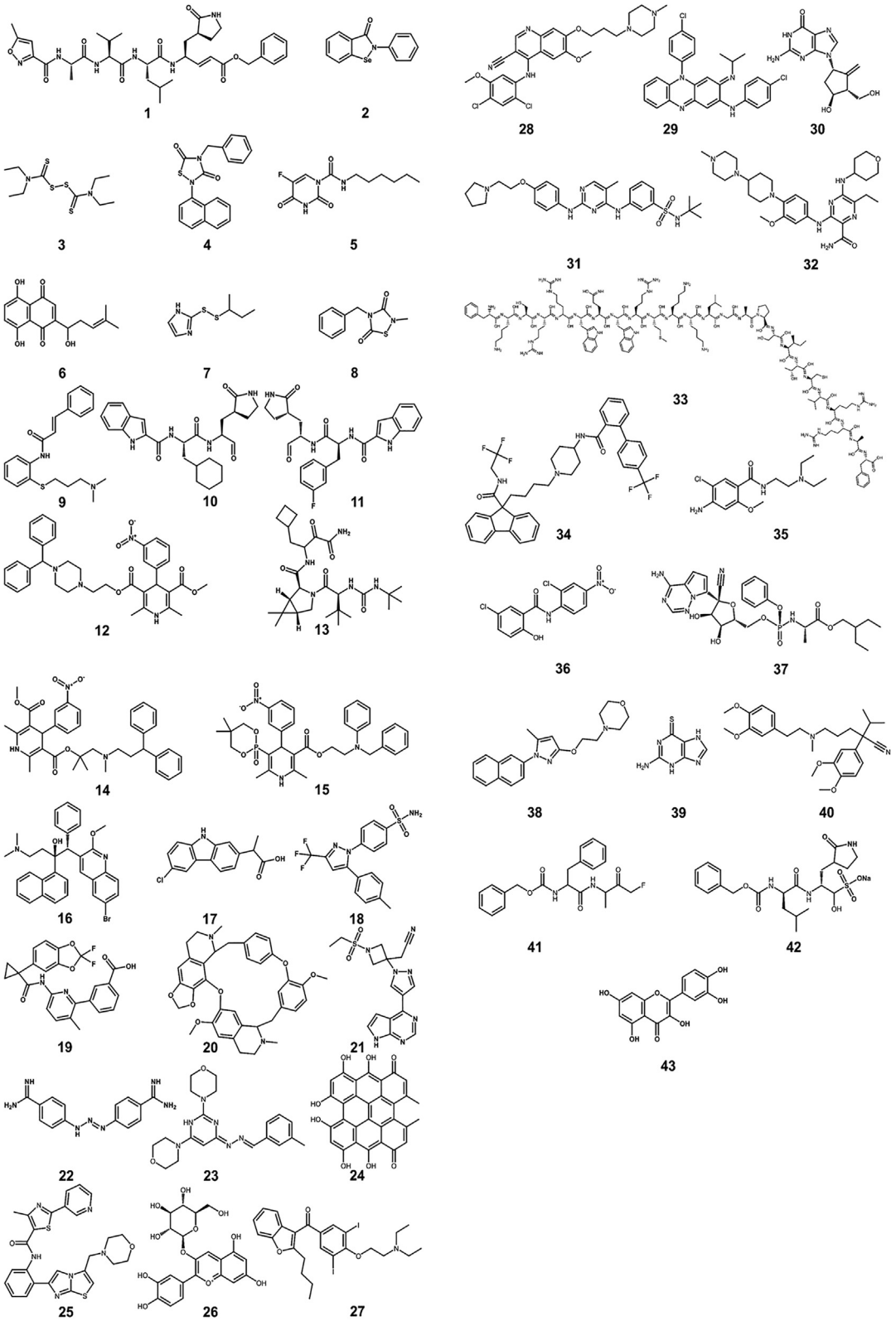

Fig. 2. Chemical structures of small molecule inhibitors and peptides that are active against the SARS-CoV-2 virus. **1**, N3, **2**, Ebselen **3**, Disulfiram **4**, Tideglusib **5**, Carmofur **6**, Shikonin **7**, PX-12 **8**, TDZD-8 **9**, Cinanserin **10**, N-((S)-3-cyclohexyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)propan-2-yl)-1H-indole-2-carboxamide **11**, N-((S)-3-(3-fluorophenyl)-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)propan-2-yl)-1H-indole-2-carboxamide **12**, Manidipine **13**, Boceprevir **14**, Lercanidipine **15**, Efonidipine **16,** Bedaquiline **17**, Carprofen **18**, Celecoxib **19**, Lumacaftor **20**, Cepharanthine **21**, Baricitinib **22**, Diminazene **23**, 4,4′-((Z)-6-(((E)-3-methylbenzylidene)hydrazono)-3,6-dihydropyrimidine-2,4-diyl)dimorpholine **24**, Hypericin **25**, Cyanidin-3-O-glucoside **26**, SRT2104 **27**, Amiodarone **28**, Bosutinib **29**, Clofazimine **30**, Entecavir **31**, Fedratinib **32**, Gilteritinib **33**, Lactoferrin (the peptide segment expected to be important) **34**, Lomitapide **35**, Metoclopramide **36**, Niclosamide **37**, Remdesivir **38**, S1RA **39**, Thioguanine **40**, Verapamil **41**, Z-FA-FMK, **42**, GC376 **43**, Quercetin. It is important to note that some of these molecules (e.g., Ebselen, Disulfiram, Carmofur, PX-12, Tideglusib, and Shikonin) could be nonspecific promiscuous compounds (see [229]).

reason behind the high infectivity of SARS-CoV-2 [243]. By performing structure-based virtual ligand screening of a library of 4,000 compounds, including approved drugs and natural products, followed by in vitro enzyme-based assay, they discovered an antiparasitic drug Diminazene **22**, that showed competitive inhibition of furin, with an IC50 of 5.42 ± 0.11 μM.

Huang et al. applied a novel biological activity-based modeling (BABM) approach to discover a compound inhibiting the SARS-COV-2 [244]. The BABM method relies on the hypothesis that compounds with similar activity patterns tend to share similar targets or mechanisms of action. In the BABM method, compound activity profiles established on a massive scale across multiple assays were used as signatures to predict compound activity in a new assay or against a new target. They first trained and validated this approach by identifying new antiviral lead candidates for Zika and Ebola based on data from ~ 0.5 million compounds screened against ~ 2,000 assays. Subsequently, BABM models were then applied to predict ~ 300 compounds not previously reported to have activity for SARS-CoV-2, which were then tested in a live virus assay exhibiting high (>30%) hit rates. The most potent compound **23** showed an IC_{50} value of 0.5 μM.

Pitsillou et al. targeted the SARS-CoV-2 M^{pro} by performing a molecular docking screen of 300 small molecules [245], which included phenolic compounds and fatty acids from the OliveNet™ library [246], and an additional group of curated pharmacological and dietary compounds. The study led to the identification of three inhibitors, hypericin **24**, cyanidin-3-O-glucoside **25,** and SRT2104 **26** that showed the IC_{50} values of 63.6 ± 5.7 μM, 65.1 ± 14.6 μM and 85.0 ± 16.8 μM, respectively, in the enzyme-linked immunosorbent assays. Also, molecular dynamics simulations further demonstrated that the lead compounds formed stable interactions with the M^{pro} active site.

Mirabelli et al., by using quantitative high-content morphological profiling and artificial intelligence-based machine learning strategy to classify features of cells for infection and stress, identified several efficacious single agents as well as combination therapies against SARS-CoV-2 [247]. This hybrid technique detected multiple antiviral mechanisms of action (MOA), including inhibition of viral entry, propagation, and modulation of host cellular responses. From a library of 1,441 FDA-approved compounds and clinical candidates, they identified 15 compounds with antiviral effects: Amiodarone **27** (EC_{50}: 52 nM), Bosutinib **28** (20 nM), Clofazimine **29** (84 nM), Entecavir **30** (42 nM), Fedratinib **31** (24 nM), Gilteritinib **32** (224 nM), Lactoferrin **33** (308 nM), Lomitapide **34** (766 nM), Metoclopramide **35** (468 nM), Niclosamide **36** (142 nM), Remdesivir **37** (97 nM), S1RA **38** (222 nM), Thioguanine **39** (22 nM), Verapamil **40** (533 nM), and Z-FA-FMK **41** (107 nM).

Hung et al. reported GC376 **42** as a potent inhibitor for the M^{pro} encoded by SARS-CoV-2, with an IC_{50} of 26.4 ± 1.1 nM, and inhibited SARS-CoV-2 replication with an EC_{50} of 0.91 ± 0.03 μM. Docking analysis revealed that the recognition and binding groups of GC376 were within the active site of SARS-CoV-2 M^{pro} [248].

Abian et al., by screening a small chemical library consisting of about 150 compounds, identified quercetin **43**, a natural product, as a reasonably potent inhibitor of SARS-CoV-2 M^{pro} (K_i ~ 7 μM). Quercetin was shown to interact with M^{pro} using biophysical techniques, and molecular docking simulations were performed to clarify the interaction of quercetin with M^{pro} [249].

In a recent and innovative study, Cao et al. targeted the interaction between the SARS-CoV-2 spike protein and the human ACE2 using de novo design approaches [250]. Computer-generated scaffolds were built around an ACE2 helix that interacts with the spike receptor-binding domain (RBD) or docked against the RBD to identify new binding modes, and subsequently, their amino acid sequences were designed to optimize the target binding, folding, and stability. Ten designed miniprotein inhibitors were found to be binding to the RBD and exhibited affinities ranging from 100 pM to 10 nM. These molecules blocked SARS-CoV-2 infection of Vero E6 cells with the IC50 values between 24 pM and 35 nM (Table 1).

4. Preparation for the next global health crises

Numerous problems about the present Covid-19 crisis have been reported by different groups [91,251–253]. We add below some of our observations.

Working in silos. Since the beginning of this crisis, hundreds/thousands of scientists in academia (e.g., in Europe) have been puzzled by the lack of a roadmap with a clear, collectively planned definition of research priorities and distribution of tasks. As a result, many projects got started in uncoordinated ways, squandering scare resources. Many researchers, supposed to be working towards the same objective, often on the same campus, could not share information nor (precompetitive) data because nobody was clearly in charge. These, most likely, led to many missed opportunities. Along the same line of reasoning, if we take the specific case of drug repositioning, in several countries in Europe, no strategies were discussed among the teams and the combination of in silico and in vitro approaches insufficiently used (or not used at all). This would have been important as compounds missed in vitro could have been identified in silico and vice versa. Definitively the lack of discussions with decision makers and the fact in silico drug designer teams were essentially ignored during this crisis is frightening.

Pain but no gain and lost in the grant application jungles while the world was dying. Another point in many countries (not directly related to Covid-19 but) and at least in academic research, has been the realization that for over 20 years, financial supports for drug discovery have been very limited. Further, drug discovery skills are often not considered in academia and thus, the scientists working in this field have usually even less chance to move on with their careers [254]. During this crisis, it was surprising to have to spend so many precious hours in writing low success-rate grants while thousands of people were dying every day. Changes seem needed.

Education and information. Explanations about drug discovery to the general population, the strengths and weaknesses of each approach (silico, vitro, animal models) and about the therapeutic agents have been essentially lacking.

Rigidity versus agility and so many unclear entry points. Delays and unnecessary bureaucracy are well-known in academia, but scientists have been told, for several decades already, that processes were going to be improved (less bureaucracy, encouraging teamwork, self-organization...). Also, in many countries (e.g., in Europe), millions of euros were spent in a myriad of fragmented projects but definitively not enough were dedicated to the development of in vitro screening platforms (i.e., the cost of developing such platforms to quickly test hypotheses is negligible as compared to the social and economic turmoil caused by the pandemic). Animal model platforms were even less available to drug hunters, even more so for computer teams. The process, if any, to test a candidate molecule with the help of an experimental platform was thus very complex with no clear entry point. This suggests that many interesting compounds (or drug combinations) could not be explored in a timely manner. Along the same line, the procedure to initiate (or to build on the results of) clinical trials, at least for approved drugs, was also very frustrating and many interesting drugs or drug combinations could not be explored in some countries because of unnecessary bureaucracy.

Table 1
Biological activity values against the SARS-CoV-2 virus of some small molecules with the corresponding protein targets.

Cpd.	Target	Biological activity	Ref. (PMID)
1 (N3)	M^{pro}	not reported	[228]
2 (Ebselen)	M^{pro}	0.67 μM	[228]
3 (Disulfiram)	M^{pro}	9.35 μM	[228]
4 (Tideglusib)	M^{pro}	1.55 μM	[228]
5 (Carmofur)	M^{pro}	1.82 μM	[228]
6 (Shikonin)	M^{pro}	15.75 μM	[228]
7 (PX-12)	M^{pro}	21.39 μM	[228]
8 (TDZD-8)	M^{pro}	2.15 μM	[228]
9 (Cinanserin)	M^{pro}	125 μM	[228]
10	M^{pro}	0.053 μM	[230]
11	M^{pro}	0.04 μM	[230]
12 (Manidipine)	M^{pro}	4.8 μM	[231]
13 (Boceprevir)	M^{pro}	5.4 μM	[231]
14 (Lercanidipine)	M^{pro}	16.2 μM	[231]
15 (Efonidipine)	M^{pro}	38.5 μM	[231]
16 (Bedaquiline)	M^{pro}	18.7 μM	[231]
17 (Carprofen)	M^{pro}	3.97%	[232]
18 (Celecoxib)	M^{pro}	11.97%	[232]
19 (Lumacaftor)	Nsp13	0.3 mM	[233]
20 (Cepharanthine)	Nsp13	0.4 mM	[233]
21 (Baricitinib)	AAK1	8.2 nM	[234,235,237]
21 (Baricitinib)	BIKE	20 nM	[234,235,237]
21 (Baricitinib)	GAK	120 nM	[234,235,237]
22 (Diminazene)	Furin and Spike protein cleavage	5.42 μM	[243]
23	Phenotypic screening	0.5 μM	[244]
24 (Hypericin)	M^{pro}	63.6 μM	[245]
25 (Cyanidin-3-O-glucoside)	M^{pro}	65.1 μM	[245]
26 (SRT2104)	M^{pro}	85.0 μM	[245]
27 (Amiodarone)	Phenotypic screen (SARS-CoV-2)	52 nM	[247]
28 (Bosutinib)	Phenotypic screen (SARS-CoV-2)	20 nM	[247]
29 (Clofazimine)	Phenotypic screen (SARS-CoV-2)	84 nM	[247]
30 (Entecavir)	Phenotypic screen (SARS-CoV-2)	42 nM	[247]
31 (Fedratinib)	Phenotypic screen (SARS-CoV-2)	24 nM	[247]
32 (Gilteritinib)	Phenotypic screen (SARS-CoV-2)	224 nM	[247]
33 (Lactoferrin)	Phenotypic screen (SARS-CoV-2)	308 nM	[247]
34 (Lomitapide)	Phenotypic screen (SARS-CoV-2)	766 nM	[247]
35 (Metoclopramide)	Phenotypic screen (SARS-CoV-2)	468 nM	[247]
36 (Niclosamide)	Phenotypic screen (SARS-CoV-2)	142 nM	[247]
37 (Remdesivir)	Phenotypic screen (SARS-CoV-2)	97 nM	[247]
38 (S1RA)	Phenotypic screen (SARS-CoV-2)	222 nM	[247]
39 (Thioguanine)	Phenotypic screen (SARS-CoV-2)	22 nM	[247]
40 (Verapamil)	Phenotypic screen (SARS-CoV-2)	533 nM	[247]
41 (Z-FA-FMK)	Phenotypic screen (SARS-CoV-2)	107 nM	[247]
42 (GC376)	M^{pro}	26.4 nM	[248]
43 (Quercetin)	M^{pro}	7 μM	[249]

Hope for the future. Definitively, we believe that these observations call for changes in the management of research in many countries. With regard to academic drug discovery, important efforts have been done, for example in the USA, with the creation of the Academic Drug Discovery Consortium or dynamic maps to develop small molecules or biologics proposed by the National Center for Advancing Translational Sciences [255–257], in UK [258,259] or in Sweden [260], to mention only a few. Of course, we are all aware that academic drug discovery is challenging and difficult to organize [261]. Yet, instead of a fragmented and very costly academic drug discovery research as presently operated in many countries, it should be possible to develop true interdisciplinary (including computational groups and many other skills required for drug discovery endeavors), coordinated and agile drug discovery networks that recognize all actors along the value chain.

5. Concluding remarks

The COVID-19 pandemic has severely affected the everyday life of humans [262]. In this mini-review, we first reported some online in silico approaches and databases that can assist the study of SARS-CoV-2. Although the race to find vaccines has been dominating the headlines, it is important to note that the search for other types of anti-viral agents is also critical. Overall, computational approaches have assisted numerous projects and in several cases proposed interesting compounds that have been validated in vitro. When time is a critical factor, combined in silico and in vitro repurposing approaches can indeed be a possible avenue but efforts on the prediction of the potential benefit of drug combination will be needed. In parallel, screening large (and high quality) compound collections (including virtual small chemical compounds and peptides) can be extremely valuable but of course the process is more time consuming. Novel, more efficient tools to predict ADMET properties and to predict the best possible targets or pathways are still needed and so are strategies that can help selecting the best treatments for a given population. These challenges do not only apply to infectious diseases but to most disease conditions. Besides assisting the identification of putative drugs, computational approaches combined with molecular biology and medicine and with biophysical methods helped to improve our understanding of several mechanisms involved in the virus life cycle, in some cases, at the atomic level. Hit-to-lead optimization of the discovered chemotypes using various in silico including

multi-parameter optimization strategies and medicinal chemistry skills are ongoing and may lead to superior ligands that could be brought to the clinics in a near future.

But to be prepared to face future global health challenges, we believe that establishing integrated academic in silico-in vitro-in vivo early drug discovery networks has to become a priority in many countries. At present, academic drug discovery research is often fragmented, while collaborations between the public and private sectors remain most of the time, in many countries, wishful thinking. Breaking silos is also going to be a major challenge for the years to come as so many skills and technologies/knowledge are needed to cost-effectively discover new drug candidates. Are we prepared for the next global health crisis (plans, structures and resources)? For the time being, the answer is no. The scientific community has done outstanding work during this crisis but the top-down management seen in many (nonprofit) organizations and in many countries has often stifled researchers' creativity and destroyed engagement.

CRediT authorship contribution statement

Natesh Singh: Formal analysis, Writing - original draft. **Bruno O. Villoutreix:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We apologize for not being able to reference all the in silico studies in this review, this is not only due to space limitation but also to the fact that thousands of articles using in silico approaches have been reported these last several months and that it is impossible to review all in a mini-review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2021.04.059.

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