# Metallo Therapeutics for COVID-19. Exploiting metal-based compounds for the discovery of new antiviral drugs.

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**Abstract**

**Introduction:** The COVID-19 pandemic, poses an unprecedented challenge for the rapid discovery of drugs against this life-threatening disease. Owing to the peculiar features of the metal centers that are currently used in medicinal chemistry, metallodrugs might offer an excellent opportunity to achieve this goal.

**Areas covered:** Two main strategies for developing metal-based drugs against the SARS-CoV-2 are herein illustrated. Firstly, a few clinically approved metallodrugs could be evaluated in patients according to a "drug repurposing" approach. To this respect, the gold drug auranofin seems a promising candidate, but some other clinically established metal compounds are worthy of a careful evaluation as well. On the other hand, libraries of inorganic compounds, featuring a large chemical diversity, should be screened to identify the most effective molecules. This second strategy might be assisted by a pathway-driven discovery approach arising from a preliminary knowledge of the mode of action, exploitable to inhibit the functional activities of the key viral proteins. Also, attention must be paid to selectivity and toxicity issues.

**Expert opinion:** The medicinal inorganic chemistry community may offer a valuable contribution against COVID-19. The screening of metallodrugs' libraries can expand the explored "chemical space" and increase the chance of finding effective anti-COVID agents.

**Keywords:** Auranofin; COVID-19; Drug Repurposing; Inorganic Pharmacology; Metal Based Drugs; SARS-CoV-2.

**Article highlights:**

- The COVID-19 pandemic spurred the international scientific community to rapidly discover effective drugs.
- Metal-based drugs have been scarcely considered so far for their potential application in fighting the SARS-CoV-2 virus.
- Owing to their large structural and chemical variety, metal-based drugs form an important arsenal for the discovery of effective agents against the SARS-CoV-2 virus.
- Some metal-based drugs have already been tested against the SARS-CoV-2 virus showing remarkable effects in contrasting virus replication and inhibiting a few key viral enzymes.

## 1. INTRODUCTION

### *1.1 Therapeutic options for COVID-19 disease*

The sudden emergence and the worldwide spreading of the COVID-19 disease pose dramatic problems to the health systems as no vaccine or truly effective drug or treatment are yet available. Vaccination is undoubtedly the most effective weapon to contrast viral infections. However, there are inherent risks with vaccination such as the possible non-complete virus inactivation or potential side effects in humans; even once a vaccine has been developed, a very accurate quality control is mandatory to make the treatment safe. Accordingly, the development of a vaccine is a very long process; a vaccine might be not available on the market even for years after the appearance of a new pathogen. For instance, despite the huge efforts made in the last decades, no effective vaccine has been developed so far for the HIV infection;

nevertheless, people that are HIV-infected experience nowadays a very high quality of life thanks to the availability of several and effective anti-HIV drugs. Analogously, the international scientific community is working intensely for the quick development of vaccines against the SARS-CoV-2 virus, but at the moment it is not possible to predict when a vaccine will be available [1]. Thus, as in the case of HIV infection, the discovery and the rapid implementation of effective antiviral drugs against SARS-CoV-2 represents an extremely important and urgent issue.

### *1.2 Molecular Targets for an effective SARS-CoV-2 therapeutics*

Accordingly, the international scientific community is working hard to find new substances capable of fighting the SARS-CoV-2 virus. To this respect, the knowledge of the virus at the molecular level is rapidly expanding and the possible druggable targets are being identified and characterized [2]. The RNA genome sequence of the SARS-CoV-2 virus, now determined (GenBank ID: MN908947.3), offers clues for the selection of the main targets and the discovery of effective treatments. Indeed, 29 distinct viral proteins were identified including 4 structural and 25 non-structural proteins. Notably, SARS-CoV-2 possesses a *spike protein* responsible for virus binding to the host cell surface receptor, i.e. the angiotensin-converting enzyme 2 (ACE2). Following cell entrance, viral RNA associates to the host ribosome to synthesize two polyproteins that are crucial for the production of new mature virions. In turn, the proteolytic cleavage of these polyproteins is performed by the coronavirus main proteinase (3CLpro) and the papain-like protease (PLpro), two viral cysteine proteases. Moreover, SARS-CoV-2 contains an RNA-dependent RNA polymerase (RdRp), responsible for replicating the RNA genome. All the above mentioned proteins are believed to represent primary druggable targets to contrast SARS-CoV-2 growth and replication, and specific efforts are being done to find molecules capable of hitting these targets selectively (Figure1) [3–5].

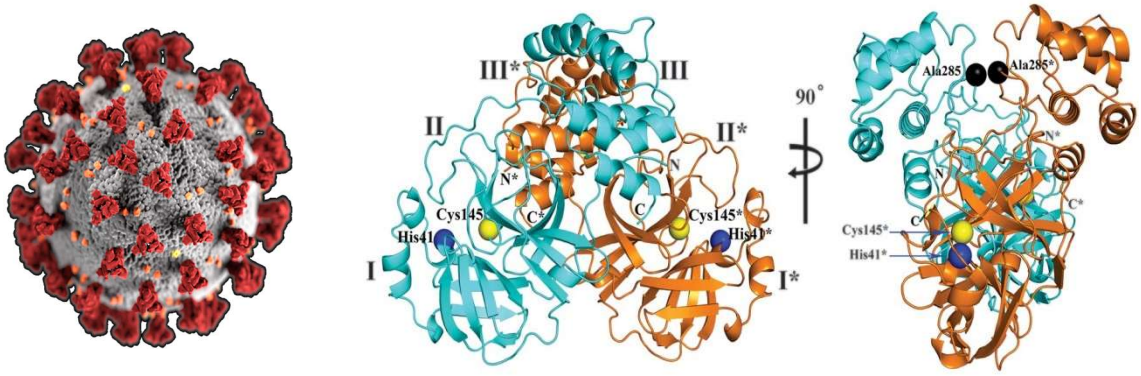


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**Figure 1.** Panel A: The ultrastructural morphology of coronaviruses (Centers for Disease Control and Prevention, United States, Department of Health and Human Services. Identification number #23312, content providers: CDC and Alissa Eckert, MSMI; Dan Higgins, MAMS, https://phil.cdc.gov/Details.aspx?pid=23312). Panel B: Three-dimensional structure of SARS-CoV-2 Mpro (also called 3CLpro); adapted from ref. 3.

A straightforward approach to disclose active compounds readily available to the clinicians to fight the COVID-19 disease is represented by drug repurposing, i.e. the use of drugs that are already in clinical use for a different therapeutic indication. An intense research activity is being carried out on libraries of FDA approved drugs, and a few promising candidates have already been identified for drug repurposing against COVID-19 disease (e.g. Tocilizumab, Chloroquine, Remdesivir) [6].

As we are working in the field of metal-based drugs, we were surprised in learning that, at the best of our knowledge, no metal compound is being tested clinically through repurposing against this disease. At the same time, even the screening of innovative metal-based drugs is very limited. We believe that important opportunities may arise from the extensive testing of metallodrugs as potential anti COVID-19 agents; reasons that corroborate this concept are reported below.

## 2. METAL-BASED DRUGS AS PROSPECTIVE ANTICOVID AGENTS

Since the antiquity, metals and metal compounds have long attracted physicians for their fascinating, nearly “magic”, properties and played accordingly a pivotal role even in the pioneering times of modern pharmacology starting from the late 19$^{th}$/early 20$^{th}$ century. Indeed, gold, bismuth, antimony and mercury compounds were widely used to treat a variety of diseases, mostly infectious, including tuberculosis and syphilis, and a number of parasitic diseases [7,8]. Even arsenicals were largely employed in the clinics at that time. Later on, these inorganic compounds were gradually abandoned because of growing (and often justified) concerns regarding their systemic toxicity and of the advent of new organic drugs often showing better pharmacological performances and a lower toxicity. Yet, some inorganic drugs are still in use in today clinical practice for a few specific applications where they play valuable and irreplaceable roles, conjugating a remarkable efficacy with an acceptable toxicity [8,9]. The most striking example is offered by the broad use of cisplatin and its analogues in cancer chemotherapy; in spite of their remarkable systemic toxicity, it can be estimated that platinum drugs are present in about 50% of current chemotherapeutic protocols for cancer treatment [9].

Their relevant toxicity may be accepted on the basis of a cost/benefit balance in relation to the extreme severity of cancer disease. In any case, there are some other cases worth of note such as antimony compounds for leishmaniasis; the use of arsenic trioxide for promyelocytic leukemia; the use of bismuth compounds to treat *Helicobacter Pylori* infections, etc. [8–10]. Notably, during the last four decades, interest in metal-based drugs, largely fuelled by the great clinical success of cisplatin, first approved by FDA in 1978, has given rise to a relatively vast and very active international scientific community working in the field of inorganic medicinal chemistry.

Chemically speaking, metal-based drugs contain a wide variety of metal centres endowed with absolutely peculiar chemical and reactivity properties, arising from the metal's electronic structure, its coordination sphere, the nature of the ligands, the oxidation state, the redox potential, etc.; it is evident that those chemical features cannot be reproduced and completely vicariated by simple organic compounds. The unique chemical and biological properties of the various metal centres –in several cases non-physiological metals- can be exploited for medical use (see Figure 2 for some relevant examples of inorganic drugs with a medicinal application) [11,12]. Metal compounds are believed to exert their cellular and biological effects by direct inhibition of enzymes, alterations of transcription factors, interaction with a variety of biomolecules through coordinative bonding, enhanced lipophilicity, alteration of cell membrane functions, interference with the cell cycle etc. Medicinally used metal compounds often possess a soft metal center, e.g., gold(I), platinum(II), silver(I), according to the Pearson HSAB theory, characterized by a large affinity for proteins and enzymes containing accessible and functionally important thiol or selenol groups.

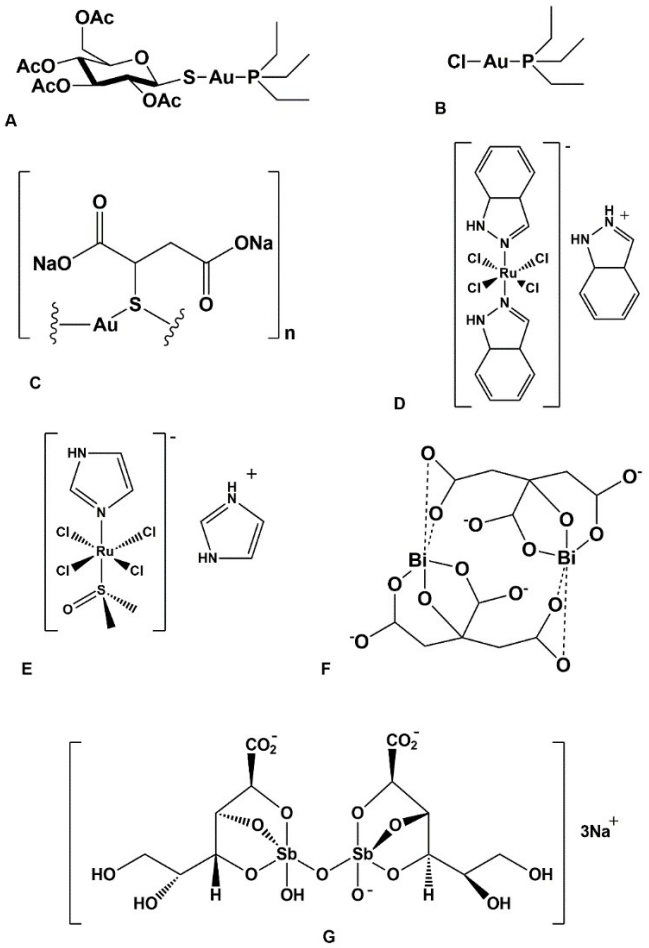


**Figure 2.** Chemical structures of auranofin (A); Chloro(triethylphosphine)gold(I) (B); Aurothiomalate (C) KP1019 (D); NAMI-A (E); Bismuth(III) citrate (F); Sodium stibogluconate (G)

In view of these arguments, we strongly encourage the international scientific community to explore systematically and rapidly the potentialities of metal compounds in drug discovery programs for COVID-19 therapeutics. In doing this, it is extremely important to take into consideration toxicity issues as metal-based drugs are generally known to produce relevant deleterious effects. Yet, prediction of toxicity for a metal compound is not easy as toxicity critically arises not only from the nature of the metal centre but also from the nature of its ligands. Assessing and/or predicting the toxicity of metal compounds is thus a very hard and complicated task as it clearly emerges from a recent and comprehensive review paper by Egorova and Ananikov appeared in Organometallics [13]. Indeed, the safety statement, must include at least two distinct kinds of toxicity assessment, acute and systemic toxicity, for which a quite wide variety of models and procedures either *in vivo* or *in vitro* or even *in silico* need to be implemented. Two main strategies to discover effective metal-based drugs for COVID-19 treatment are illustrated in the following sections.

### *2.1 Strategies to discover effective metallodrugs for COVID-19 disease*

### *2.1.1 Drug discovery through repurposing of clinically established metal-based drugs*

As stated above, a straightforward approach to discover effective metallodrugs for COVID-19 disease is given by the repurposing of metal-based drugs, clinically approved for other therapeutic indications, against the COVID-19 disease. The great advantage of this approach is given by the fact that no detailed toxicological analysis is warranted as this information is already available in previous literature at least to some sufficient extent. There are a number of approved metal-based drugs with promising features and an acceptable toxicity profile that might be considered for repurposing. Particularly attractive seem to be those metallodrugs bearing a soft metal centre capable of binding tightly to free thiol groups of target proteins [14,15]. To this end, we are supporting a rapid evaluation of a clinically established gold(I) drug, i.e. auranofin [2,3,4,6-tetra-o-acetyl-L-thio-β-D-glycol-pyranoses-S-(triethyl-phosphine)-gold(I)] (brand name is Ridaura®), AF hereafter [16]. Reasons that support this recommendation are summarized below. AF is a simple gold(I) drug, orally administered, with remarkable antinflammatory properties approved by the FDA on 1985, for the treatment of rheumatoid arthritis. Its mechanism of action is not completely understood yet, but there is evidence that it is capable of interfering with immune response pathways. More recent studies revealed that the mechanism of action of AF involves induction of redox dysregulation and severe intracellular oxidative stress, both mediated by inhibition of thioredoxin reductase and induction of mitochondrial disfunction [17,18]; inhibition of the proteasome and endoplasmic reticulum stress were described as well. In recent years AF has attracted growing interest for drug repurposing as an anticancer agent or for the treatment of Schistosomiasis and other infectious diseases [17,18]. Also, it turned active against HIV and was included in clinical trials as an antiretroviral agent [19]. Importantly, AF is more effective than hydroxychloroquine against HIV infections; moreover, its enhanced activity is associated with a more favourable pharmacokinetic profile [17,18,20,21].

Analogously to tocilizumab, AF is capable of interfering and blocking interleukin-6 signalling pathways through phosphorylation of JAK1 and STAT3 [22]. Furthermore, AF shows a potent inhibitory activity toward selected proteases (in particular the cysteine proteases) arising from its ability to coordinate tightly to proteins bearing free cysteine residues [23]. On the ground of these motivations, a rapid off-label evaluation of auranofin as an antiviral agent for the treatment of COVID-19 patients is highly recommended.

This proposal is now strengthened by very recent *in vitro* evidences -appeared during the writing of this paper- that AF inhibits potently SARS-CoV-2 replication while attenuating inflammation in human cells [24]. In their work Kumar *et al*. first infected Huh7 cells (hepatocyte-derived

carcinoma cell line) with SARS-CoV-2 virus; next, cells were treated with 4 μM of AF and, as well as supernatants, sampled at increasing time intervals (24 and 48 h). Virus RNA copies were measured using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). Overall, AF treatment significantly reduced the viral RNA in the supernatant (70%) after 24 h. Remarkably, at the 48 h time point, this percentage was even higher (85%). Intracellular viral RNA decreased by 85% after 24 hours, while a 95% reduction was detected after 48 hours (see figure 3, panel A). Also, auranofin was well tolerated by Huh7 cells at the tested concentrations. Results highlighted that auranofin inhibited the replication of SARS-CoV-2 in the infected cells with an $EC_{50}$ of about 1.5 μM [24]. The same authors demonstrated that AF is capable of reducing the expression of SARS-CoV-2-induced cytokines in Huh7 cells. SARS-CoV-2 infection induce a high increase of mRNA expression of IL-6 that may result in severe lung inflammation phenomena; at variance only a 2-fold increase in expression of IL6 was found in the cells treated with auranofin (figure 3, panel B) [24]. Altogether these results strongly support the suitability of AF for COVID-19 treatment.

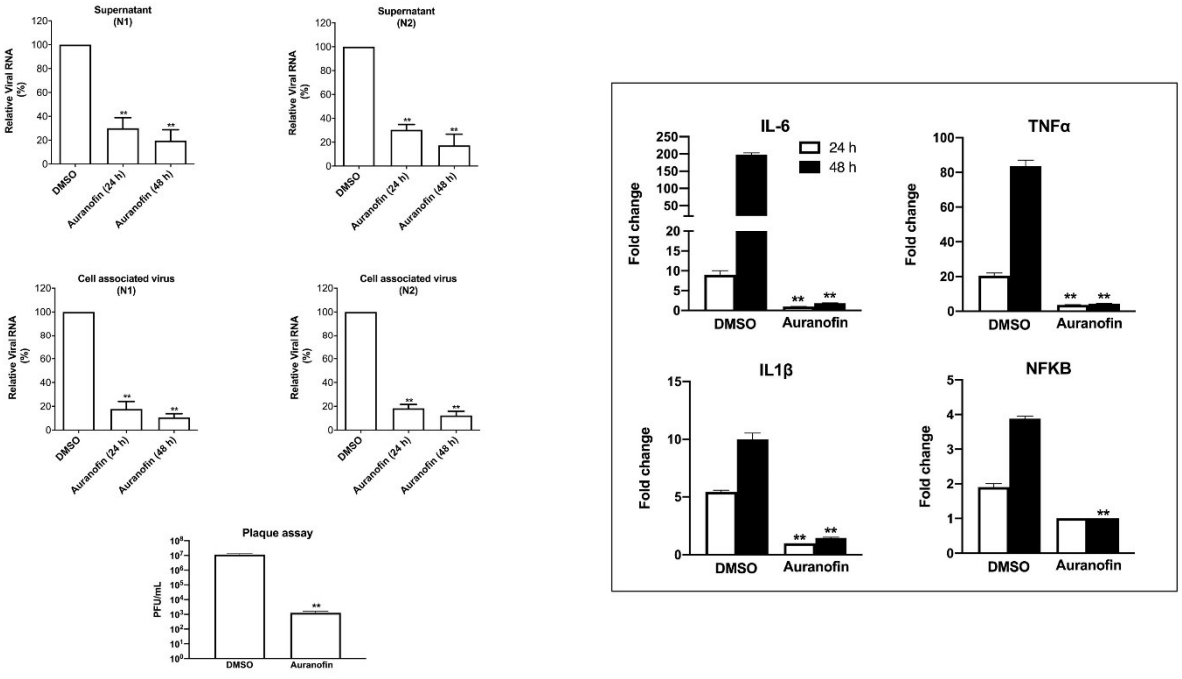


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**Figure 3.** Panel A: Auranofin (4 μM) inhibits replication of SARS-COV-2 in Huh7 cells infected with SARS-COV-2 (viral RNA levels measured by RT-PCR using primers and probe targeting the SARS-COV-2 N1 region and the SARS-COV-2 N2 region). SARS-COV-2 infectivity titers were measured in cell culture supernatants at 48 h after infection by plaque assay. Data represent the mean ± SEM, representing two independent experiments conducted in duplicate, t-test $p < 0.001$. Panel B: Auranofin

treatment reduced the expression of SARS-COV-2-induced cytokines in human cells: mRNA levels of IL-6, IL-1β, TNFα and NF-kB were determined by qRT-PCR at 24 and 48 h after infection. Data are the mean ± SEM (two independent experiments conducted in duplicate). Adapted from ref. 24.

Such drug repurposing strategy that we propose for AF could be well extended to some other clinically established gold drugs for rheumatoid arthritis, such as aurothiomalate (Figure 2C) and aurothioglucose. The AF analogue, chloro(triethylphosphine)gold(I), AF-Cl hereafter, where the thiosugar moiety is replaced by a simple chloride ligand (Figure 2B) is another promising candidate for repurposing. AF-Cl is commercially available and has been clinically tested in comparison with AF for the treatment of arthritis [25]. Notably AF-Cl, through the pharmacologically active cation $[Et_3PAu]^+$, is able to bind the catalytically relevant His133 residue of cyclophilin models [26]. This latter feature is of particular interest considering that some molecules interacting with cyclophilin A have been selected as promising drug candidates against COVID-19 [6].

Also, a few clinically approved bismuth and antimony compounds (Figure 2F and 2G) showing peculiar reactivity properties and a strongly thiophilic character together with an acceptable toxicity profile, should be included in this kind of evaluation. It is worthy reminding that Hongzhe Sun *et al.,* a few years ago, extensively investigated the properties of bismuth compounds against the SARS-CoV virus [27–29]. Some of those compounds were particularly effective in inhibiting the helicase and protease catalytic activities of the SARS-CoV virus. In particular, they found that a series of Bi-based complexes bearing N, O-containing polydentate ligands including porphyrin complexes are featured by potent inhibition activities against helicase ATPase ($IC_{50}$ of about 0.5 μM) [28]. Interestingly, the comparison of the inhibitory activity of the complexes bearing different ligands -inherently associated with a different stability- revealed that the bismuth centre plays a key role in producing the inhibitory effects. The SARS helicase duplex-unwinding induced by bismuth-based complexes was also measured and the porphyrin complexes resulted the most effective in inhibiting helicase unwinding activity to the duplex gradually upon the addition of increasing concentrations [28].

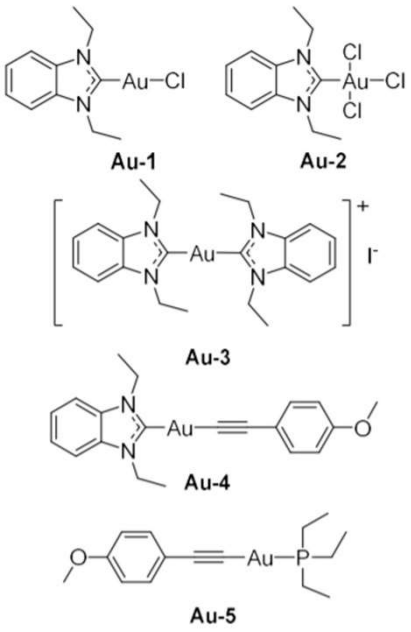
Very recently, the inhibitory potency of some bismuth salts in clinical use, namely bismuth potassium citrate (CAS No. 57644-54-9), ranitidine bismuth citrate (CAS No. 128345-62-0) and bismuth citrate (CAS No. 813-93-4) was reported toward the NTPase and RNA helicase activities of non-structural SARS-CoV-2 nsp13 protein, that plays an important role in SARS-CoV-2 virus replication. This finding points to nsp13 as an additional druggable target for new antiviral agents [30].

Beyond bismuth, also the experimental anticancer ruthenium compounds NAMI A and KP1339 might be good candidates for anti-COVID 19 testing; NAMI A and KP1339 were previously admitted to clinical trials for cancer treatment and were shown to be quite safe at relatively high concentrations [31]. Later on, NAMI A was discharged from clinical trials due to limited anticancer efficacy in the selected cancer model. Now, studies are underway to assess the efficacy of these ruthenium compounds in inhibiting SARS-CoV-2 replication *in vitro*.

### *2.1.2 Drug discovery through the screening of libraries of metal-based compounds*

In our opinion, extensive *in vitro* testing of large and representative libraries of metal-based agents of medicinal interest against SARS-CoV-2 replication is highly warranted. Investigational panels should mainly include families of medicinally suitable metal-based agents showing an acceptable toxicity profile. Bismuth, ruthenium, and antimony compounds owing to their relatively safe toxicity profiles might be optimal candidates. A number of organometallic compounds of medicinal interest could be also included in the investigational panel. Indeed, though none of them has received so far clinical approval [32], several organometallic compounds comprising a variety of different metals have been prepared and characterized in recent years and shown to be very promising in terms of pharmaceutical action; the presence of at least one direct carbon-metal bond usually stabilizes the metal center toward redox changes. However, a careful analysis of their toxicity profile should be preventively performed.

The potential interest on this latter class of metallodrugs has now been confirmed by I. Ott and coworkers in a recent paper appeared in ChemRxiv™ public repository [33]. A small panel encompassing three well known and two newly synthesized gold organometallics was tested to assess the ability of these gold compounds to impair the viral entry process through the inhibition of the interaction between the SARS-CoV-2 spike and ACE2 receptor. More in detail the panel included the 5 compounds shown in figure 4 and auranofin for reference purposes. Generally, the tested compounds turned effective in impairing this key step of the infection process despite some large differences in the relative potency emerged. In addition, the panel compounds were analyzed for their ability to inhibit the PLpro activity and low micromolar $IC_{50}$ values were indeed measured in most cases.




A

| | spike-ACE2 ($IC_{50}$, μM) | PLpro ($IC_{50}$, μM) |
|---|---|---|
| benzimidazole | > 100 | > 100 |
| Chloroquine | 31.9 ± 5.4 | n.d. |
| Disulfiram | n.d. | 6.5 ± 0.4 |
| Auranofin | 22.2 ± 2.8 | 25.5 ± 1.2 |
| **Au-1** | 19.4 ± 5.7 | 6.3 ± 1.6 |
| **Au-2** | 20.0 ± 2.3 | 5.5 ± 0.5 |
| **Au-3** | 21.3 ± 6.8 | 14.2 ± 0.3 |
| **Au-4** | 25.0 ± 4.2 | 14.1 ± 2.1 |
| **Au-5** | 16.2 ± 2.4 | 6.7 ± 0.9 |

B

**Figure 4.** Panel A: the gold drugs studied by Ott and co-workers. Panel B: values for the inhibition of the spike-ACE2 interaction and PLpro activity. Adapted from ref. 33.

Owing to the relatively large affinities for the two above mentioned targets, these gold organometallic compounds are presumed to be potent inhibitors of the virus replication process [33].

More in general, relatively large panels of metallic compounds should be considered for screening including series of structurally related metal complexes; the various metal compounds could be ranked according to their antiviral potency and useful structure activity relationships might be drawn. This kind of screening might be further assisted by the study of the inhibitory properties of the panel complexes toward selected viral targets that seem to be crucial for virus survival and replication such as the two main proteases (i.e. 3CLpro and PLpro) and the RNA polymerase (RdRp). This type of information might lead to some sort of pathway-driven or target driven discovery approach. In particular, a strong inhibition of viral cysteine proteases by metal compounds containing highly soft and thiophilic metal centers such as gold(I), antimony(III) and bismuth(III) may well be anticipated based on HSAB considerations. On the other hand, Ruthenium compounds are predicted to bind preferentially to solvent exposed imidazole residues and thus block functionally relevant histidine residues [34–36]. Also, the chance that metal compounds may cause relevant changes in the host cell, e.g. induction of oxidative stress,

hindering virus invasion and replication should be taken into consideration as a realistic antiviral mechanism.

## 3. CONCLUSIONS

We have shown here that metal based drugs feature a large variety of chemical structures and reactivities strictly linked to the nature of the metal center and of the surrounding ligands. Owing to such large chemical variety it is quite obvious to consider metal compounds, at least in principle, as a rich source of novel medicinally useful substances; accordingly, we strongly recommend that metal-based drugs are included as much as possible in new drug discovery screening programs. This may be particularly relevant in the search of novel agents to treat COVID-19 disease, a severe and rapidly spreading disease for which medical treatments are not yet available and are urgently needed. Two main strategies have been considered to develop metal-based drugs as anti-COVID-19 agents: drug repurposing and new drug discovery. Concerning the first approach some very encouraging results have been reported at least *in vitro* for Auranofin, a gold compound in clinical use for the treatment of rheumatoid arthritics. Analogously, some bismuth compounds seem very promising. The second type of approach is certainly more complex and time consuming but might offer greater opportunities; it might be assisted by pathway-driven or target driven discovery considerations. Pros and Cons of the two drug discovery strategies are analyzed and critically discussed.

## 4. EXPERT OPINION

Metal based drugs form a relatively small but highly peculiar class of pharmacological substances that includes a large variety of metal centers and structural motifs. Despite the long tradition in the use of metal compounds in pharmacology dating back to the early times of modern pharmacology, this group of drugs has experienced in the last decades some decline in interest and in clinical use owing to well-grounded concerns regarding their systemic toxicity. However, the various metal centers possess unique chemical properties that may be exploited successfully against specific pharmacological targets and selected diseases; thus some inorganic drugs are still in clinical use with important roles due to the occurrence of specific pharmacological actions that cannot be achieved with the usual organic drugs (see the case of anticancer platinum drugs). Some other inorganic compounds have been rediscovered as potent antiparasitic drugs.

When a new severe disease appears for which there are no effective medical treatments as it is the case of COVID-19 disease, all the possible therapeutic opportunities must be explored. We believe that inclusion of a large array of metal-based agents in the screening libraries and programs may significantly expand the chemical space and increase the chance of finding effective drugs. In doing this, some favorable properties intrinsic to the metal centers such as the Lewis acidity and the soft character may provide an “added value” that is not found in standard organic compounds. Thus, we may expect that medicinal inorganic chemistry may offer a significant contribution to the fight against COVID-19. It may be hypothesized that so many unusual and unique metal centers may hopefully produce some important and favorable effects on this new pathogen that are difficult to predict *a priori* and may lead to the rapid identification of clinically useful substances. Indeed, a first analysis of the main druggable targets of SARS-CoV-2 highlights the presence of a few enzymes, in particular two crucial cysteine proteases and the helicase, that might be optimal targets for compounds bearing soft metal centres. Notably, a few preliminary results suggest that selected gold and bismuth compounds are able to produce a strong inhibition of those catalytic activities thus contrasting very effectively virus replication.

Undoubtedly, the conspicuous systemic toxicity generally associated to the mentioned metals remains a major problem though a large variability in the toxicological profiles of metallic compounds is typically observed. In any case, to overcome toxicity issues and obtain substances of quick clinical implementation it may be advisable to take advantage of the so called “drug repurposing strategies” where metal compounds already in clinical use -and for which the toxicological profile is known- are tested for a new therapeutic indication. Accordingly, repurposing strategies might be extended to many metal compounds that are still in clinical use or that were in clinical use in the past. Testing may be well extended to a few metal compounds that are currently undergoing clinical trials (e.g. anticancer ruthenium compounds). Moreover, it should be reminded that the suggested use of these drugs for COVID-19 patients’ treatment is not for a chronic use. This may avoid those long-term side effects that usually limit the clinical application of metallodrugs. Careful cost/benefit analyses might facilitate their use. Also, rapid preliminary tests might be oriented in assessing whether at a safe dose the considered metal compounds are therapeutically active in COVID-19 patients. Basically, there is at present an almost complete lack of these crucial data that may ensure the safe use of metal-based drugs against SARS-CoV-2.

Also, a more classical approach of new drug discovery concerning metal substances might be implemented where libraries of metal-based compounds are tested first *in vitro*, then *in vivo* in appropriate animal models of the disease. This type of approach is far more expensive in time and money; however, due to the impressive progresses in the design and synthesis of new metal complexes, this latter approach may lead to optimized metal compounds in terms of target recognition and overall pharmacological and toxicological profile that might turn excellent antiviral drugs.

**Funding**

This manuscript has not been funded.

**Acknowledgements**

D.C. gratefully thanks Fondazione Italiana per la Ricerca sul Cancro (AIRC) for the financial support (two-years fellowship “Marcello e Rosina Soru”, project code: 23852). The authors thank the CIRCMSB (Consorzio Interuniversitario di Ricerca in Chimica dei Metalli nei Sistemi Biologici), Italy. Beneficentia Stiftung (Vaduz, Liechtenstein) and Fondazione CR Firenze (Firenze, Italy) are also acknowledged.

**Declaration of interest**

Authors declare no conflict of interest.

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