5

Exploiting the Chemical Diversity of Metal Compounds as a Source of Novel Anti-COVID-19 Drugs

Damiano Cirri[1], Tiziano Marzo[2], Carlo Marotta[1], Alessandro Pratesi[1,*] and Luigi Messori[3,*]

[1]Department of Chemistry and Industrial Chemistry, Via Giuseppe Moruzzi 13, 56124 Pisa, Italy. alessandro.pratesi@unipi.it
[2]Department of Pharmacy, University of Pisa, Via Bonanno Pisano 6, 56126 Pisa, Italy.
[3]Department of Chemistry 'Ugo Schiff', University of Florence, Via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy. luigi.messori@unifi.it

Contents

ABSTRACT 2
1. METAL SUBSTANCES AS A RICH SOURCE OF DRUGS 3
2. THE COVID-19 DISEASE: SOME GENERAL REMARKS 6
3. METAL COMPOUNDS AS POTENTIAL ANTI-COVID-19 AGENTS: A FEW REMARKABLE EXAMPLES 10
   3.1. AURANOFIN 11
   3.2. SILVER SULFADIAZINE 12
   3.3. $[Co(ACACEN)(NH_3)_2]Cl$ 13
   3.4. BISMUTH COMPOUNDS 14
4. TOWARD A MORE SYSTEMATIC APPROACH IN THE SEARCH FOR METAL-BASED DRUGS FOR COVID-19 DISEASE 15
   4.1. SELECTION OF METALLODRUGS FOR THE SCREENING 16
   4.2. ASSESSMENT OF METAL COMPOUNDS AS INHIBITORS OF THE INTERACTION BETWEEN THE S PROTEIN AND THE ACE2 RECEPTOR 17
   4.3. ASSESSMENT OF METAL COMPOUNDS AS INHIBITORS OF THE PAPAIN-LIKE PROTEASE 18
   4.4. ASSESSMENT OF METAL COMPOUNDS AS ANTI-SARS-COV-2 AGENTS 18
5. CONCLUSIONS 20
6. ABBREVIATIONS 21
7. REFERENCES 23

Abstract

The outbreak of the COVID-19 pandemic has triggered the strong and urgent need of finding new effective drugs against the SARS-CoV-2 virus. Despite the intense efforts made by the international scientific community in the course of the last two years and some initial success, this issue remains absolutely open. Metal-based agents form a class of substances possessing a large variety of chemical structures and reactivities that may result in innovative and unprecedented modes of action. This class of substances merits to be explored in the search of effective antiviral agents. In this short review, we offer some examples of the possible role of metal-based drugs as prospective anti-COVID-19 agents. Particular attention is paid to a few established gold and bismuth compounds that looked very promising in some preliminary tests of antiviral efficacy. In addition, we illustrate a systematic strategy proposed very recently by Ott *et al.* for the rational discovery of promising antiviral drug candidates within relatively large libraries of metal compounds. Notably, implementation of this strategy has already resulted in the identification of a few metal compounds endowed with interesting features suitable for further pharmacologic development. Overall, we aim to underscore the valuable role that medicinal inorganic chemistry may play in the search and discovery of new anti-COVID-19 drugs.

KEYWORDS:

Metal-based drugs, COVID-19, SARS-CoV-2, gold, bismuth, POMs

1. Metal substances as a rich source of drugs

Metals and, in general, inorganic compounds have been used for medicinal purposes for centuries [1]; this mostly occurred on an empirical basis until the end of the 19th and the beginning of the 20th century. This latter period coincides, indeed, with the first steps of modern pharmacology. At that time, metal salts and some metal- or metalloid-based substances, that were already part of the available therapeutic arsenal, started to be systematically investigated for potential application against several diseases, in particular bacterial and parasitic ones [2–6]. As a result of those pioneering studies, many inorganic molecules entered therapeutic protocols and have played afterward, at least for a few decades, a pivotal role in the medical treatment of infections. It is emblematic and historically important the case of the discovery of Salvarsan® by the Nobel laureate Paul Ehrlich (1910) for the treatment of syphilis and, two years later, of the more soluble Neosalvarsan® (1912). Until this discovery, syphilis often represented a deadly infection that was mainly treated with mercury and potassium salts (e.g. KI), with quite poor clinical results [5]. Alongside, bismuth-based molecules were also used for the treatment of syphilis because of the lower toxicity of bismuth compounds compared with arsenicals. Similarly, in more recent times, a few infections caused by *Entamoeba histolytica* (amebiasis) or *Trichomonas vaginalis* have been treated with organoarsenical compounds [5]. These observations altogether underline the significant role of metal compounds in the early times of modern pharmacology.

Later on, in 1965, the discovery and the subsequent FDA approval (1978) of cisplatin, represented the beginning of a new era in the treatment and management of cancer where metal compounds still play a central role [7–9]. Indeed, following the huge clinical success of this small platinum inorganic drug, the international research community started to investigate several different transition metals for the synthesis and the evaluation of novel and improved drug candidates for the treatment of various types of cancers [6,10,11]. In fact, despite the large clinical success of cisplatin-based treatment protocols, anticancer Pt compounds are generally accompanied by the

occurrence of severe side effects for the patients as well as the frequent insurgence of resistance phenomena [12]. Nephrotoxicity, hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhoea, and alopecia are only some of the negative side effects which often emerge after cisplatin administration; similarly, the treatment, especially when prolonged, can become ineffective due to acquired resistance [12]. In this frame, the second and third-generation platinum anticancer drugs, i.e., carboplatin and oxaliplatin, were developed with subsequent worldwide approval in 1989 and 2001 respectively [13].

Figure 1.

The two latter drugs were basically developed as cisplatin analogues, but are characterized by a greater tolerability owing to their relatively small but functionally relevant structural differences [13,14]. While cisplatin and carboplatin possess pharmacological profiles that are substantially superimposable, oxaliplatin is instead used, almost exclusively, to treat colorectal cancer for which it is far more efficacious than cisplatin and carboplatin [13,15]. This significant difference in terms of therapeutic actions is unlikely to depend on the interaction with a single biological target. At variance, most probably, while DNA remains a biologically relevant target for the anticancer profiles of all three Pt drugs, in the case of oxaliplatin, additional mechanisms and additional targets are most likely operative. Notably, a recent paper by Lippard and coworkers pointed out that in this latter case, induction of ribosome biogenesis stress is functionally relevant for oxaliplatin, but not for cisplatin, in order to trigger cancer cell death [16]. In this context, it can be affirmed that even small changes in the ligands coordinated to the metal ions may have a large impact on the mechanism of anticancer platinum metallodrugs [17]. Beyond platinum, several transition metals and metalloids have been exploited in the last decades in an attempt to obtain improved inorganic drugs. Among them, some ruthenium, gold, titanium, copper, iridium, bismuth, arsenic or tellurium compounds revealed promising medicinal properties and are the subject of further studies

[6,11,16,18]. Figure 2 reports some of these important inorganic drugs that are currently used to treat a variety of diseases, additional ones can be seen *e.g.* in chapters 1 and 4 in this book.

Figure 2.

In the last years, a number of reasons have prompted a renewed interest in inorganic medicinal chemistry. Prior to then, the development of modern synthetic techniques in organic chemistry during the 20th century, and the discovery of important organic drugs (e.g. Penicillins, Zidovudine) had impacted significantly and positively the clinical treatment of diseases, contributing to a substantial decrease in the overall interest for inorganic drugs. However, in some therapeutic areas such as that of antibacterial agents, quite rapidly, the reduced rate of discovery of new organic drugs, and the insurgence of bacterial resistance, determined the need for novel drugs and triggered the development of innovative drug discovery strategies [1,2,19]. Among the various strategies that have been developed, a reliable and effective one is represented by the reappraisal of approved or established inorganic drugs [1,20,21]. This trend has been further spurred in recent times by the emergence of modern omics technologies capable of providing in-depth insights into the mechanism of action of new metal-based compounds [22–25]. In turn, these innovative methods have allowed researchers to approach the drug design issue using a mechanism-oriented approach. Similarly, this increasing knowledge concerning the relevant pathways for the pharmacological activity of inorganic drugs can be conveniently applied in the frame of the "drug repurposing" strategy [1].

The latter approach, which relies on the use of established/already approved drugs for a therapeutic indication different from the original one, is suitable in all the fields of medicine but may become fundamental in a few selected cases. Specifically, it may be conveniently exploited for the implementation of treatments against neglected diseases (see also chapter 7 which describes advances in metal-based agents to treat neglected diseases) as well as diseases for which new drugs

are highly needed owing to their huge social and economic impact at a global level. Examples of the first case are tropical or endemic diseases that represent a major health problem in some countries (Africa, Asia, and Latin America in particular). In this frame, the use of already FDA approved drugs represents a suitable option, because of the need for drugs that are quickly available and at a low cost. Moreover, the repurposed drugs are safe since they have already been extensively studied and approved for different clinical applications. The second case typically refers to diseases that have a high impact worldwide and are among the first causes of death, such as cancer. Additionally, drug repurposing may turn extremely important in the case of sudden and unexpected sanitary emergencies where the fast introduction of effective drugs in clinical settings is absolutely needed [20,26].

This latter situation is clearly exemplified by the COVID-19 pandemic as discussed below. This chapter, which builds on the comprehensive findings showcased in chapter 4, is specifically aimed at demonstrating how the field of metal-based drugs may offer a valid contribution to the search and identification of novel and effective substances capable of fighting this sudden, unexpected and severe viral disease.

2. The COVID-19 disease: some general remarks

Between the end of 2019 and the beginning of 2020, in Wuhan, China, a new virus belonging to the coronavirus family suddenly appeared and rapidly began to spread worldwide. The associated disease was soon qualified as a global pandemic health emergency. The causative pathogen was described by the International Committee on Taxonomy of Viruses as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 caused an outbreak of unprecedented viral pneumonia in the Hubei area. Despite many attempts to contain its spreading, this novel coronavirus, due to the very high transmission rate, broke the borders of that area rapidly. In

February 2020, the disease was announced as COVID-2019 by the World Health Organization (WHO) [26]. Looking at the WHO reports (see for further details https://www.who.int/), the dramatic impact of the COVID-19 is evident. For instance, estimates suggest that the number of global deaths attributable to the COVID-19 pandemic by the end of 2020 was already, at least, 3 million. Nowadays, with the development of successful vaccines, we have effective weapons against the SARS-CoV-2; yet, the virus is continuing to significantly impact health systems in several countries worldwide. In addition, the continuous spreading of the virus causes its mutation in new variants ~~for~~ which the vaccines, based on the original SARS-CoV-2 virus that emerged in Wuhan (China), may be less effective (e.g. Omicron) [27].

Fever, cough, headache, exhaustion, breathing difficulty, loss of smell and loss of taste are some of the symptoms of COVID-19. Symptoms may appear one to fourteen days following the viral contact. However, around a third of the infected people show no signs or symptoms. The majority (81%) of those who manifest symptoms noticeable enough to be classified as patients have mild to moderate symptoms (up to mild pneumonia), whereas 14% have severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% have critical symptoms (respiratory failure, shock, or multiorgan dysfunction) [28]. Older and immune-compromised people are at a greater risk of developing severe forms of this disease. Some people continue to experience a range of effects for months after recovery (the so-called “long COVID”), and significant damage to organs has been observed. Multi-year studies are underway to further investigate the long-term effects of the disease.

The SARS-CoV-2 virus is spread through the air when droplets and minute airborne particles harboring the virus are inhaled. When people are close together, the risk of transmission is greatest; nonetheless, transmission can occur across longer distances, especially indoors. Transmission also occurs if contaminated fluids are splashed or sprayed into an individual's eyes, nose, or mouth, or via contaminated surfaces. Even if they do not exhibit symptoms, people might be contagious for up to 20 days and spread the virus.

Various COVID-19 testing methods are available to diagnose the disease. The standard diagnostic method directly detects the virus's nucleic acid by real-time reverse transcription polymerase chain reaction (rRT-PCR).

Several effective COVID-19 vaccines have been licensed and disseminated in nations where major immunization campaigns have taken place. Physical or social separation, quarantining, ventilation of indoor spaces, covering coughs and sneezes, hand washing, and keeping unclean hands away from the face are some more preventive strategies. In public places, the use of face masks or coverings has been advocated to reduce the risk of transmission. While medications to suppress the virus are being developed, the primary treatment remains symptomatic. Treatment of symptoms, supportive care, isolation, and experimental techniques are all part of disease management.

Already a lot of information has been garnered concerning the SARS-CoV-2 virus, the causative agent of COVID-19 disease. The SARS-CoV-2 virus is a single-stranded RNA virus. It belongs to a family of so-called coronaviruses, being part of the Coronaviridae family (order Nidovirales). The four genera of this subfamily are Alpha, Beta, Delta, and Gamma-Coronaviruses (CoVs). The sequence of SARS-CoV-2 is 96% identical to that of the bats' coronavirus. This evidence is the basis of the assumption that bats are the main reservoir for this virus. SARS-CoV-2 may cause a severe respiratory tract disease that, especially in the presence of comorbidities, may lead to critical symptoms and a poor prognosis [26,29].

Figure 3.

As also outlined in chapter 4, the infection process of SARS-CoV-2 toward human cells (host) occurs through virus binding to the cell surface protein angiotensin-converting enzyme 2 (ACE2) that is mediated by the Receptor Binding Domain (RBD) of its spike (S) glycoprotein (Figure 3).

Furthermore, the cellular transmembrane serine protease 2 (TMPRSS2) is essential for triggering the S glycoprotein. Virus entry in the host cell may also depend on the endosomal/lysosomal cysteine proteases cathepsin B and L (CTSB, CTSL), though their activity seems not to be indispensable. Recently, it was found that furin protease plays a role in the infection process. Indeed, SARS-CoV-2 contains a furin cleavage site in the S protein that is unusual for coronaviruses, and the cellular receptor neuropilin-1 (NRP1, which binds furin-cleaved substrates) potentiates SARS-CoV-2 infectivity toward the central nervous system. Additionally, SARS-CoV-2 is capable of exploiting the putative alternative receptor CD147 (expressed in high levels in the brain) to infect the central nervous system [30–33].

Retrospectively, one can assess that other coronaviruses have earlier caused outbreaks of fatal human pneumonia. Examples are the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The SARS-CoV infection emerged in the Chinese province of Guangdong in 2003 spreading to other countries and infecting more than 8000 people with more than 700 deaths [34]. At variance, the so-called MERS-CoV spread from the Middle East in 2012, reaching other countries. Based on official data, MERS-CoV infected about 2500 people, making more than 800 victims [34]. The fatality rate for SARS-CoV was lower compared with MERS-CoV being respectively estimated to be 10% and 35% [35]. The viral components of the coronaviruses, even in the case of SARS-CoV-2, represent suitable druggable targets for virus inactivation and for the development of effective therapies against the COVID-19 disease [36].

Notably, no effective drugs were available to treat COVID-19 at the time of its appearance. However, based on the information at the molecular level concerning the mechanisms involved in the viral infection that was quickly obtained, it was possible to identify a few viral proteins that are validated druggable targets. Thanks to this information since the very beginning of the pandemic, several approved drugs were screened and evaluated. Some of them entered clinical trials and were immediately tested in COVID-19 patients [37]. In any case, as suggested by WHO, curative drugs

have not been discovered yet and novel and effective antiviral agents are absolutely needed worldwide [38]. We are convinced that inorganic drugs may offer important opportunities to reach this goal. Accordingly, some of the efforts sustained by the medicinal inorganic chemistry community in this direction are illustrated in the following sections.

3. Metal compounds as potential anti-COVID-19 agents: a few remarkable examples

As previously noted, medication repurposing, i.e., the use of pharmaceuticals that are already in clinical use for a different therapeutic indication, is a straightforward strategy to make active drugs safely and easily available to clinicians for COVID-19 treatment. Accordingly, at the onset of the pandemic, intensive research was conducted on libraries of FDA-approved medications, and a few potential candidates for drug repurposing against COVID-19 were identified (e.g. Tocilizumab, Chloroquine, Remdesivir) [39–41]. We believe that important opportunities for the discovery of new and effective anti-COVID-19 agents may also arise from the repurposing as well as *de novo* testing of metal-based compounds. Indeed, metal-based compounds offer advantages over organic compounds in terms of their structural diversity and wide ranging reactivities that may well translate into drugs with innovative and unprecedented modes of antiviral action. Already, a number of studies, though not systematic, have been conducted on metal-based compounds as potential agents against SARS-CoV-2 and other viruses; these studies are comprehensively summarised in chapter 4. In this chapter, we highlight a systematic strategy for the rational discovery of promising antiviral drug candidates within relatively large libraries of metal compounds. We include reference, in particular, to the following metal compounds: auranofin, silver sulfadiazine, the cobalt compound $[Co(acacen)(NH_3)_2]Cl$, and a few related bismuth compounds. While the first three

complexes are also reviewed in chapter 4, we refer to them here also to emphasize the merits of exploiting metal-based drugs as an alternative source to organic drugs for COVID-19 treatment.

3.1. Auranofin

Undoubtedly, one of the most promising candidates for COVID-19 treatment is auranofin, a linear gold(I) complex containing triethylphosphine and tetracetylthioglucose as coordinating ligands (its chemical structure is shown in Figure 2A). Auranofin is a gold drug approved by the FDA in 1985 for the treatment of severe forms of rheumatoid arthritis [37]. This drug was soon proposed for screening against SARS-CoV-2 owing to its intriguing pharmacological features [42]. First of all, regarding its therapeutic profile as an anti-arthritic agent, it displays a high tolerance and a relatively low systemic toxicity [43,44]. It is well accepted that its mechanism of action mainly involves the inhibition of the key redox enzyme thioredoxin reductase (TrxR), a selenoenzyme that is responsible for the entire cellular redox balance [45]. This feature, likewise, plays a key role for auranofin's activity against the SARS-CoV-2 infection. In fact, Kumar and co-workers recently demonstrated that TrxR inhibition in cells infected with virions of the CoV family down-regulates, in turn, the synthesis of key proteins of SARS-CoV-2 [46–48]. Hence, auranofin could indeed be considered as a promising candidate to treat this infection. Furthermore, regarding its general antiviral properties as outlined in chapter 4, auranofin has previously displayed efficacy against the HIV, [49] being tested in clinical trials as an antiretroviral agent [50].

Notably, the potential activity of auranofin toward the SARS-CoV-2 virus was rapidly confirmed in a study conducted on human hepatocellular carcinoma derived cell line (Huh7) [51]. In this study, auranofin was found to inhibit the replication of the virus by 95% after 48 h at low μM concentration, whilst it was well tolerated by the tested cells. In addition, auranofin proved to be able to reduce the inflammation in the same panel of cells by decreasing the expression, promoted by the SARS-CoV-2 infection, of the cytokine IL-6. This occurrence is important because the infection typically promotes an over-expression of the mRNA of IL-6 which results in diffuse lung

inflammation [51]. Noteworthy, in a different study, auranofin also proved to inhibit the interaction between the active center of the ACE2 enzyme and the spike protein of the virus, which, as mentioned above, is a central pivot for the access of the virus into the cell [52]. In addition, auranofin was also reported to potently inhibit the papain-like protein (PL^{pro}) of SARS-CoV-1 and SARS-CoV-2, a key enzyme for the replication of the virus [52]. In summary, these results, also taking into account the additional anti-viral properties associated with auranofin outlined in chapter 4, strongly support the potential role of auranofin in the treatment of COVID-19 infection [37] and therefore warrant further experimentation.

3.2. Silver sulfadiazine

In the frame of metal-based drug repositioning, some attempts have also been made to assess the potential of silver in the treatment of SARS-CoV-2 infection. Indeed, the antibacterial properties of silver have been known for a long time [53]. For example, the commercially available drug silver sulfadiazine (brand name SOFARGEN®) associates the activity of the silver ion with the antibacterial activity of the sulfadiazine drug and this combination is commonly used as a topical antimicrobial [54]. In contrast, the antiviral activity of this class of compounds has not been studied as much as their antimicrobial properties. However, silver sulfadiazine had been previously demonstrated to manifest antiviral activity against HIV and the herpesvirus [55,56]. As for the SARS-CoV-2 infection, silver nanoparticles were confirmed to have antiviral activity against this virus [57]. Moreover, research demonstrated the ability of three silver-based compounds (namely silver nitrate, silver sulfadiazine and Ag-3) (Figure 4) to inhibit PL^{pro} at μM concentration. In particular, all the three species displayed IC_{50} values in the μM range against SARS-CoV-2 PL^{pro}, whereas their activity was lower against SARS-CoV PL^{pro}, proving the selectivity of these compounds for the SARS-CoV-2 PL^{pro} enzyme. Noteworthy, Ag-3 displayed a strong inhibitory activity (in the μM range) against SARS-CoV-2. For these three compounds it has been postulated

that their activity might be directly linked to the presence of the silver(I) ion itself, as suggested by the fact that silver nitrate has a similar activity to the other two compounds [58].

Figure 4.

3.3. [Co(acacen)(NH_3)$_2$]Cl

Another druggable target of the virus is the SARS-CoV-2 main protease (M^{pro}) (also called $3CL^{pro}$) [59–65], against which cobalt-containing compounds have been explored. Indeed, reports have suggested that some regions of this protein might be blocked through the interaction of cobalt(III)-cations with its histidine and cysteine residues, ultimately deactivating the protease [59]. In particular, among all the histidine residues of the protein, His41 represents an interesting target as metal-ion binding to its imidazole side chain might disrupt the H-bonds of the protein, thus deactivating the enzyme [65]. One candidate that was proposed for this purpose is [Co(acacen)(NH_3)$_2$]Cl (Figure 5), which was also reported to be able to inhibit other proteases by targeting the imidazole ring on the His side chain [66,67]. In fact, if an excess of [Co(acacen)(NH_3)$_2$]Cl is used, the binding to at least three histidine residues could be observed [65]. Consequently, similarly to another study of Co(III) binding to the myoglobin protein [68], the binding of the metal compound to this large number of histidines might render the surface of the protein more hydrophilic, thus resulting in its unfolding. In the same way, copper(II) chelates, due to their ability to inhibit a thrombin protease have also been explored for this purpose [69]. Indeed, some complexes were proved to be able to dock to His41 and Cys145 amino acid residues of the M^{pro} protein [65]. In particular, [(meta-amidinosalicylidene-l-alaninato)copper(II)]Cl (Figure 5) was successfully docked near His41 and it is possible that little motions of the protein might allow the

binding of Cu(II) to the Cys145 thiolate, thus disrupting the protein functionality. Other less bulky analogues were also docked into the Cys145 site and the results led to similar consideration [65].

Figure 5.

3.4. Bismuth compounds

Bismuth compounds form another class of drugs with promising properties against the SARS-CoV-2 virus. Indeed, in studies conducted against SARS-CoV, some of them proved to be able to inhibit the protease and helicase catalytic activities of the virus, which are vital for its life [70–72]. Noteworthy, a panel of compounds endowed with N,O-containing polydentate ligands showed potent inhibitory activity against helicase ATPase (IC_{50} in the range of μM) (figure 6) [71]. By comparing the activity of these compounds, it was possible to conclude that the bismuth center plays a crucial role in their activity. Notably, among all the tested complexes, the porphyrin ones turned out to be the most potent in inhibiting the activity of helicase [71]. Regarding the SARS-CoV-2 infection, some bismuth complexes that are currently used in clinical practice, i.e., bismuth citrate, ranitidine bismuth citrate and bismuth potassium citrate (their chemical structures, together with additional bismuth-based compounds, are shown in Figure 6. Also, Figure 2 shows the chemical structure of the stable dinuclear unit of the so-called bismuth potassium subcitrate, were evaluated for their inhibitory capabilities against the NTPase and RNA helicase activities of non-structural nsp13 protein, a fundamental protein for the replication of SARS-CoV-2 [73]. In addition, the activity of ranitidine bismuth citrate, Figure 6, was investigated both *in vitro* and *in vivo*, with very promising results in both cases. On the one hand, in the *in vitro* tests, not only did it display a low toxicity and high selectivity, but also turned able to inhibit the viral helicases [74]. This finding validated previous reports on the relevance of this protein as a target for the virus and on the

capability of this complex to target it [43,75]. On the other hand, in the animal model investigated, it drastically reduced the replication of the virus, which ultimately results in a diminished viral load on the pulmonary system of the tested animals [74]. Furthermore, although these complexes haven't been studied in clinical trials so far, a report showed that administration of bismuth subsalicylate was able to improve the conditions of a patient with Crohn's disease whose conditions had been worsened by the SARS-CoV-2 infection. In particular, this therapy markedly diminished the cough and diarrhoea of the patient and improved their appetite [76].

Recently published results presented noticeable preclinical anti-SARS-CoV-2 efficacy of a cocktail therapy consisting of clinically used bismuth-based drugs, e.g., colloidal bismuth subcitrate or bismuth subsalicylate, and N-acetyl-L-cysteine [77].

Figure 6.

4. Toward a more systematic approach in the search for metal-based drugs for COVID-19 disease

The examples described above provide solid evidence that metal compounds may play an important role in the medical treatment of COVID-19 and, as such, should be intensely investigated in the search for new antiviral agents. However, more systematic and more effective drug discovery strategies in the field of metal-based drugs need to be implemented.

In this regard, we highlight a seminal study by Ott *et al.* in an attempt to define a more rational approach for the identification of metal-based substances that might manifest important antiviral actions and might be suitable for further pharmaceutical development [58].

Notably, the strategy proposed by Ott and coworkers includes the following steps:

i) selection of metallodrugs for the screening;

ii) assessment of metal compounds as inhibitors of the interaction between the S protein and the ACE2 receptor;

iii) assessment of metal compounds as inhibitors of the papain-like protease;

iv) assessment of metal compounds as anti-SARS-Cov-2 agents.

It is evident that this strategy is grounded on the concept that the spike protein and the papain-like protease are primary druggable targets for the development of new antiviral substances. The details of each step of this strategy are illustrated below.

4.1. Selection of metallodrugs for the screening

Ott *et al.* exploited an extensive library of metal compounds, featuring large chemical diversity, in their study, supported by the participation of many European laboratories with specific expertise in the field of inorganic synthesis and metal-based drugs. Indeed, about ten distinct laboratories took part in this effort. More specifically, the panel of studied metal compounds included 93 mononuclear compounds and 11 polyoxometalates (POMs). The mononuclear complexes contained many different transition metals, mainly Au, Ru and Fe, but also Rh, Ag, Pt, Pd, Ti and others, as already discussed in chapter 4. Some of the compounds included in the panel as potential anti-SARS-CoV-2 agents were polyoxometalates (POMs) bearing metal or metalloid centers such as As, Co, Pb, Sn, W, and Ge among others. Basically, this family of metal-oxide cluster compounds is featured by a wide range of structures that have been reported as to provide effective anticancer, antiviral and antibacterial agents (see figure 7) [78–83]. Specifically, their proven ability to inhibit viral replication are relevant for our purposes here [84–86]. Indeed, the possible recognition of the S protein of coronavirus by polyoxometalates has been recently highlighted [87].

Figure 7.

4.2. Assessment of metal compounds as inhibitors of the interaction between the S protein and the ACE2 receptor

This step concerns the screening of the panel compounds for their ability to inhibit the interaction of the spike protein with the Angiotensin-Converting Enzyme-2 (ACE2) receptor; the observation of a strong inhibition may well be predictive of potent antiviral activity. As described in detail in section 2, the S protein plays a key role in the early phases of infection; it primarily mediates virus entry into the host. This viral protein is capable of binding toward the ACE2 on the cell membrane of the host. These considerations clearly delineate the S protein as an exploitable druggable target to block the entry of the virus and, as a consequence, the infection cascade [88–91]. Furthermore, the S1 subunit of the S protein is featured by the presence of the so-called receptor-binding domain (RBD). This domain is capable of tightly binding the N-terminal helix of ACE2 in turn allowing the viral attachment. Noteworthy, the receptor-binding domain contains nine cysteine residues forming four disulphide bonds [92] representing exploitable targets for metallodrugs or metal fragments, preventing the cellular entry of SARS-CoV-2.

The ELISA test was the reference method by which the panel of inorganic drugs was assessed for their ability to impair the S/ACE2 recognition and the associated binding process. Overall, the mononuclear complexes were inactive or only scarcely active in these tests. Indeed, an inhibition ranging from 25 to 50% was reported only in a small number of tested molecules including some gold, ruthenium, iron and platinum-based complexes (e.g. cisplatin). In this frame, the only exception was titanocene dichloride, characterized by an inhibition percentage of about 69%.

At variance, better results were obtained with POMs; in seven cases, an inhibitory activity >50% of the S/ACE2 recognition process was observed. Based on these results, four compounds were selected for further studies as the best performers including titanocene dichloride (its chemical structure is shown in Figure 2G) and three POMs (POM-6, POM-7, POM-11 in Figure 7).

4.3. Assessment of metal compounds as inhibitors of the papain-like protease

Proteases are exploitable targets for the design and implementation of new antiviral agents. In fact, their impairment may lead to the blockade of the viral life and of the replication cycle without affecting the host. With a view to developing effective inorganic anti-SARS-CoV-2 agents, given the fact that the papain-like protease (PL^{pro}) and the 3-chymotrypsin-like protease ($3CL^{pro}$, even known as M^{pro}) are crucial for viral replication, these proteases are suitable targets for the design and testing of specific antiviral drugs against SARS-CoV-2 [93–95]. Interestingly, the sequence of SARS-CoV-2 PL^{pro} is very similar (about 83%) to that of SARS-CoV which was responsible for the sudden outbreak of the SARS epidemic in 2003. The two viruses share domains of the papain-like protease that are very similar. Specifically, the two domains are known as the putative labile zinc-binding domain and the catalytic cysteine cleavage domain, which bear druggable cysteines [52,94,96]. Notably, a number of panel compounds, in particular auranofin, aurothiomalate, a few triphenylphosphine gold compounds and many POMs, produced potent inhibition of this viral protease [52,58,97].

4.4. Assessment of metal compounds as anti-SARS-Cov-2 agents

For the selection of suitable drug candidates against SARS-CoV-2, an important feature of the drug is that it is well tolerated by the host cells. In other words, the drug should possess a certain degree of selectivity toward the virus, so that the treatment impairs the viral infection and virus replication without causing undesirable side reactions and associated side effects. Accordingly, before the evaluation of the efficacy of a selected drug in SARS-CoV-2 infected cells, it is necessary to assess the effects (and toxic effects) of the selected molecule in suitable cell models such as Caco-2 and CaLu-3 cell lines [98]. Indeed, the best candidates for further drug development should be metallodrugs characterized by high tolerability and no significant toxic effects. Ott and coworkers reported that, among the investigated complexes, some mononuclear gold and titanium-based drugs, including aurothiomalate and titanocene dichloride, showed a suitable antiviral profile featured by

good tolerability even at the highest tested doses (500 μM). Among POMs, some compounds were very toxic in the above cell models and, accordingly, were not suitable for further assessment, while other POMs were tolerated up to tested doses of 200 μM. Beyond the tolerability in cell lines, other aspects were evaluated including solubility. Putting together all these preliminary evaluations, some compounds showing no or reasonable toxic effects, a good capability to bind the viral targets and a suitable solubility profile were selected for the evaluation in SARS-CoV-2 infected Caco-2 cells. Upon combining all the results obtained, a small panel of drug candidates emerged containing titanocene dichloride (Figure 2C), one silver-based complex (Ag-3 in Figure 4) and a POM (POM-11 in Figure 7) as well as aurothiomalate and three additional gold-based agents (Figure 8).

Figure 8.

For comparative purposes, Remdesivir was used as a reference in these tests because of its ability to impair viral replication at low micromolar doses. It is important to highlight the strategy delineated by Ott *et al*. features a smart and systematic approach for screening structurally diverse metal-based compounds. As a matter of fact, the screening of large panels of metallodrugs with established and reliable methods may conveniently support the selection of inorganic drugs endowed with both strong inhibitory profile toward the S/ACE2 recognition process and satisfactory tolerability and chemico-physical profile. Overall, at the end of the in-cell screening, it was possible to recognize three compounds as the most promising candidates, i.e., Au-12, Ag-3 and POM-11. All three featured antiviral activity falling in the range of μM. Beyond the selection of the above drug candidates, this investigation pointed out that, through systematic screening of a large panel of inorganic drugs featured by a wide chemical diversity, it is possible, using reliable methods, to select promising drug candidates against SARS-CoV-2 infection. This also makes clear that metallodrugs and, more in general, inorganic molecules may well be considered for the

development of novel and effective agents against the virus, hopefully leading to novel and improved treatments for COVID-19 disease.

5. Conclusions

Metal-based drugs form an intriguing class of potential therapeutic agents with very interesting and attractive chemical and biological properties. Here we have tried to delineate the role that metal-based drugs may play against COVID-19 on the ground of the available literature evidence from the very first empirical attempts to the design of more systematic drug discovery strategies. We have shown that metallodrugs, and more in general inorganic drugs, offer the chance to finely tune, through an appropriate molecular design approach, their chemico-physical profiles, their reactivity and thus their pharmacological profile. For instance, by varying the metal center it is possible to drive the reactivity toward selected biological substrates bearing residues with a greater affinity for that metal center. Similarly, it is possible to control the stability and the reactivity of the same metal center through the choice of proper ligands.

Thus, the proposal to screen a panel of inorganic drugs in the search of candidates against SARS-CoV-2 appears to be well supported, allowing to conveniently expand the “chemical space” for novel and improved antiviral agents. Accordingly, it is highly recommended that inorganic drugs are included in new drug discovery screening programs.

In this frame, both the strategies relying on drug reprofiling or on the assessment of newly synthesized inorganic drugs are exploitable. From the first strategy, some interesting results have already emerged for the gold(I)-based compound auranofin. Similarly, bismuth-based drugs have been evaluated against SARS-CoV-2 with promising results. The design and the testing of newly synthesized molecules is inherently more complex. However, it may offer the interesting opportunity of synthesizing compounds in a rational manner because of the increasing information

on the virus, available at the molecular level. Additionally, the inclusion of novel metallodrugs in large screening programs may offer the opportunity to further expand the chemical libraries, providing further opportunities for drug discovery. Noteworthy, even the problems associated with the systemic toxicity associated with the use of metals and metalloids may be overcome through the drug repurposing approach, thus using approved inorganic drugs, as well as through selecting newly synthesized compounds featured by the accomplishment of specific requirements in terms of selective reactivity toward the desired biological substrates and stability. Finally, considering that drugs for the treatment of COVID-19 patients are not for chronic use, it is reasonable to assess that long-term side effects might be avoided. This further contributes to the chance of widening the range of clinical applications for inorganic drugs [37].

6. Abbreviations

$3CL^{pro}$: 3-chymotrypsin-like protease

ACE2: angiotensin-converting enzyme 2

Caco-2: Immortalized human colorectal adenocarcinoma cells

CaLu-3: Non-small-cell lung cancer cell line

CoVs: Alpha, Beta, Delta, and Gamma-Coronaviruses

CTSB: Cysteine proteases cathepsin B

CTSL: Cysteine proteases cathepsin L

ELISA: Enzyme-Linked Immunosorbent Assay

MERS-CoV: Middle East Respiratory Syndrome Coronavirus

M^{pro}: SARS-CoV-2 main protease

NRP1: Cellular receptor neuropilin-1

PL^{pro}: Papain-like protein

POMs: Polyoxometalates

RBD: Receptor Binding Domain

rRT-PCR: Real-time reverse transcription polymerase chain reaction

S: Spike

SARS-CoV: Severe acute respiratory syndrome coronavirus

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

TMPRSS2: Cellular transmembrane serine protease 2

TrxR: thioredoxin reductase

WHO: World Health Organization

7. REFERENCES

1. D. Cirri, F. Bartoli, A. Pratesi, E. Baglini, E. Barresi, T. Marzo, *Biomedicines* **2021**, *9*, 504.

2. J. A. Lemire, J. J. Harrison, R. J. Turner, *Nat. Rev. Microbiol.* **2013**, *11*, 371–384.

3. N. P. E. Barry, P. J. Sadler, *Chem. Commun.* **2013**, *49*, 5106–5131.

4. N. P. E. Barry, P. J. Sadler, *Pure Appl. Chem.* **2014**, *86*, 1897–1910.

5. M. Patra, G. Gasser, N. Metzler-Nolte, *Dalt. Trans.* **2012**, *41*, 6350–6358.

6. E. J. Anthony, E. M. Bolitho, H. E. Bridgewater, O. W. L. Carter, J. M. Donnelly, C. Imberti, E. C. Lant, F. Lermyte, R. J. Needham, M. Palau, P. J. Sadler, H. Shi, F. X. Wang, W. Y. Zhang, Z. Zhang, *Chem. Sci.* **2020**, *11*, 12888–12917.

7. T. Marzo, G. Ferraro, A. Merlino, L. Messori, in *Encycl. Inorg. Bioinorg. Chem.*, Wiley, **2020**, pp. 1–17.

8. B. Rosenberg, L. VanCamp, J. E. Trosko, V. H. Mansour, *Nature* **1969**, *222*, 385–6.

9. S. M. Cohen, S. J. Lippard, in *Prog. Nucleic Acid Res. Mol. Biol.*, **2001**, pp. 93–130.

10. K. D. Mjos, C. Orvig, *Chem. Rev.* **2014**, *114*, 4540–4563.

11. T. Marzo, D. La Mendola, *Inorganics* **2021**, *9*, 46.

12. R. Oun, Y. E. Moussa, N. J. Wheate, *Dalt. Trans.* **2018**, *47*, 6645–6653.

13. T. Marzo, L. Messori, D. La Mendola, *Curr. Top. Med. Chem.* **2021**, *21*, 2435–2438.

14. T. C. Johnstone, K. Suntharalingam, S. J. Lippard, *Chem. Rev.* **2016**, *116*, 3436–3486.

15. D. Cirri, S. Pillozzi, C. Gabbiani, J. Tricomi, G. Bartoli, M. Stefanini, E. Michelucci, A. Arcangeli, L. Messori, T. Marzo, *Dalt. Trans.* **2017**, *46*, 3311–3317.

16. P. M. Bruno, Y. Liu, G. Y. Park, J. Murai, C. E. Koch, T. J. Eisen, J. R. Pritchard, Y.

Pommier, S. J. Lippard, M. T. Hemann, *Nat. Med.* **2017**, *23*, 461–471.

17. T. Marzo, A. Pratesi, D. Cirri, S. Pillozzi, G. Petroni, A. Guerri, A. Arcangeli, L. Messori, C. Gabbiani, *Inorganica Chim. Acta* **2018**, *470*, 318–324.

18. Y. Gothe, T. Marzo, L. Messori, N. Metzler-Nolte, *Chem. Commun.* **2015**, *51*, 3151–3153.

19. L. Chiaverini, A. Pratesi, D. Cirri, A. Nardinocchi, I. Tolbatov, A. Marrone, M. Di Luca, T. Marzo, D. La Mendola, *Molecules* **2022**, *27*, DOI 10.3390/molecules27082578.

20. T. Marzo, S. Taliani, S. Salerno, F. Da Settimo, E. Barresi, D. La Mendola, *Curr. Top. Med. Chem.* **2021**, *21*, 2767–2770.

21. T. Marzo, D. Cirri, S. Pollini, M. Prato, S. Fallani, M. I. Cassetta, A. Novelli, G. M. Rossolini, L. Messori, *ChemMedChem* **2018**, *13*, 2448–2454.

22. J. Sharma, L. Balakrishnan, S. Kaushik, M. K. Kashyap, *Front. Bioeng. Biotechnol.* **2020**, *8*, 829.

23. F. Magherini, T. Fiaschi, E. Valocchia, M. Becatti, A. Pratesi, T. Marzo, L. Massai, C. Gabbiani, I. Landini, S. Nobili, E. Mini, L. Messori, A. Modesti, T. Gamberi, *Oncotarget* **2018**, *9*, 28042–28068.

24. T. Gamberi, A. Pratesi, L. Messori, L. Massai, *Coord. Chem. Rev.* **2021**, *438*, 213905.

25. G. Scalese, K. Kostenkova, D. C. Crans, D. Gambino, *Curr. Opin. Chem. Biol.* **2022**, *67*, 102127.

26. P. Tarighi, S. Eftekhari, M. Chizari, M. Sabernavaei, D. Jafari, P. Mirzabeigi, *Eur. J. Pharmacol.* **2021**, *895*, 173890.

27. E. Callaway, *Nature* **2022**, *607*, 18–19.

28. NIH, "Clinical Spectrum | COVID-19 Treatment Guidelines," can be found under

https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/, **2021**.

29. X. Li, T. Li, H. Wang, *Exp. Ther. Med.* **2021**, *21*, 3.

30. Y. Wang, Y. Hao, S. Fa, W. Zheng, C. Yuan, W. Wang, *Front. Bioeng. Biotechnol.* **2021**, *9*, 849.

31. I. P. Trougakos, K. Stamatelopoulos, E. Terpos, O. E. Tsitsilonis, E. Aivalioti, D. Paraskevis, E. Kastritis, G. N. Pavlakis, M. A. Dimopoulos, *J. Biomed. Sci. 2021 281* **2021**, *28*, 1–18.

32. M. Hoffmann, H. Kleine-Weber, S. Pöhlmann, *Mol. Cell* **2020**, *78*, 779-784.e5.

33. L. Cantuti-Castelvetri, R. Ojha, L. D. Pedro, M. Djannatian, J. Franz, S. Kuivanen, F. van der Meer, K. Kallio, T. Kaya, M. Anastasina, T. Smura, L. Levanov, L. Szirovicza, A. Tobi, H. Kallio-Kokko, P. Österlund, M. Joensuu, F. A. Meunier, S. J. Butcher, M. S. Winkler, B. Mollenhauer, A. Helenius, O. Gokce, T. Teesalu, J. Hepojoki, O. Vapalahti, C. Stadelmann, G. Balistreri, M. Simons, *Science (80-.).* **2020**, *370*, 856–860.

34. Y. Yang, F. Peng, R. Wang, K. Guan, T. Jiang, G. Xu, J. Sun, C. Chang, *J. Autoimmun.* **2020**, *109*, 102434.

35. T. M. Abdelghany, M. Ganash, M. M. Bakri, H. Qanash, A. M. H. Al-Rajhi, N. I. Elhussieny, *Biomed. J.* **2021**, *44*, 86–93.

36. G. Kanimozhi, B. Pradhapsingh, C. Singh Pawar, H. A. Khan, S. H. Alrokayan, N. R. Prasad, *Front. Pharmacol.* **2021**, *12*, 638334.

37. D. Cirri, A. Pratesi, T. Marzo, L. Messori, *Expert Opin. Drug Discov.* **2021**, *16*, 39–46.

38. C. T. R. Vegivinti, K. W. Evanson, H. Lyons, I. Akosman, A. Barrett, N. Hardy, B. Kane, P. R. Keesari, Y. S. Pulakurthi, E. Sheffels, P. Balasubramanian, R. Chibbar, S. Chittajallu, K. Cowie, J. Karon, L. Siegel, R. Tarchand, C. Zinn, N. Gupta, K. M. Kallmes, K. Saravu, J. Touchette, *BMC Infect. Dis.* **2022**, *22*, 107.

39. I. O. Rosas, N. Bräu, M. Waters, R. C. Go, B. D. Hunter, S. Bhagani, D. Skiest, M. S. Aziz, N. Cooper, I. S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D. J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, A. Malhotra, *N. Engl. J. Med.* **2021**, *384*, 1503–1516.

40. A. Cortegiani, G. Ingoglia, M. Ippolito, A. Giarratano, S. Einav, *J. Crit. Care* **2020**, *57*, 279–283.

41. R. L. Gottlieb, C. E. Vaca, R. Paredes, J. Mera, B. J. Webb, G. Perez, G. Oguchi, P. Ryan, B. U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R. H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F. M. Marty, M. J. Katz, A. A. Ginde, S. M. Brown, J. T. Schiffer, J. A. Hill, *N. Engl. J. Med.* **2022**, *386*, 305–315.

42. T. Marzo, L. Messori, *ACS Med. Chem. Lett.* **2020**, *11*, 1067–1068.

43. K. Ioannou, M. C. Vlasiou, *BioMetals* **2022**, DOI 10.1007/s10534-022-00386-5.

44. W. F. Kean, L. Hart, W. W. Buchanan, *Rheumatology* **1997**, *36*, 560–572.

45. M. B. Harbut, C. Vilchèze, X. Luo, M. E. Hensler, H. Guo, B. Yang, A. K. Chatterjee, V. Nizet, W. R. Jacobs, P. G. Schultz, F. Wang, *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 4453–4458.

46. T. S. Fung, D. X. Liu, *Front. Microbiol.* **2014**, *5*, 296.

47. K. L. Siu, C. P. Chan, K. H. Kok, P. C. Y. Woo, D. Y. Jin, *Cell Biosci.* **2014**, *4*, 1–9.

48. H. A. Rothan, M. Kumar, *Pathogens* **2019**, *8*, 148.

49. R. S. Diaz, I. L. Shytaj, L. B. Giron, B. Obermaier, E. della Libera, J. Galinskas, D. Dias, J. Hunter, M. Janini, G. Gosuen, P. A. Ferreira, M. C. Sucupira, J. Maricato, O. Fackler, M. Lusic, A. Savarino, *Int. J. Antimicrob. Agents* **2019**, *54*, 592–600.

50. "Multi Interventional Study Exploring HIV-1 Residual Replication: a Step Towards HIV-1 Eradication and Sterilizing Cure - Full Text View - ClinicalTrials.gov," can be found under https://clinicaltrials.gov/ct2/show/NCT02961829?cond=Multi+Interventional+Study+Exploring+HIV-1+Residual+Replication%3A+a+Step+Towards+HIV-1+Eradication+and+Sterilizing+Cure&draw=2&rank=1, **n.d.**

51. H. A. Rothan, S. Stone, J. Natekar, P. Kumari, K. Arora, M. Kumar, *Virology* **2020**, *547*, 7–11.

52. M. Gil-Moles, U. Basu, R. Büssing, H. Hoffmeister, S. Türck, A. Varchmin, I. Ott, *Chem. – A Eur. J.* **2020**, *26*, 15140–15144.

53. H. D. Betts, C. Whitehead, H. H. Harris, *Metallomics* **2021**, *13*, 1.

54. L. C. Cancio, *Surg. Infect. (Larchmt).* **2021**, *22*, 103–112.

55. T. W. Chang, L. Weinstein, *J. Infect. Dis.* **1975**, *132*, 79–81.

56. R. E. F. De Paiva, A. Marçal Neto, I. A. Santos, A. C. G. Jardim, P. P. Corbi, F. R. G. Bergamini, *Dalt. Trans.* **2020**, *49*, 16004–16033.

57. F. Pilaquinga, J. Morey, M. Torres, R. Seqqat, M. de las N. Piña, *Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology* **2021**, *13*, e1707.

58. M. Gil-Moles, S. Türck, U. Basu, A. Pettenuzzo, S. Bhattacharya, A. Rajan, X. Ma, R. Büssing, J. Wölker, H. Burmeister, H. Hoffmeister, P. Schneeberg, A. Prause, P. Lippmann, J. Kusi-Nimarko, S. Hassell-Hart, A. McGown, D. Guest, Y. Lin, A. Notaro, R. Vinck, J. Karges, K. Cariou, K. Peng, X. Qin, X. Wang, J. Skiba, Ł. Szczupak, K. Kowalski, U. Schatzschneider, C. Hemmert, H. Gornitzka, E. R. Milaeva, A. A. Nazarov, G. Gasser, J. Spencer, L. Ronconi, U. Kortz, J. Cinatl, D. Bojkova, I. Ott, *Chem. – A Eur. J.* **2021**, *27*, 17928–17940.

59. J. J. Kozak, H. B. Gray, R. A. Garza-López, *J. Inorg. Biochem.* **2020**, *211*, 111179.

60. B. A, C. S, Z. H, L. T, B. M, *Bioinformation* **2020**, *16*, 404–410.

61. S. Das, S. Sarmah, S. Lyndem, A. Singha Roy, *J. Biomol. Struct. Dyn.* **2021**, *39*, 3347–3357.

62. R. Islam, M. R. Parves, A. S. Paul, N. Uddin, M. S. Rahman, A. Al Mamun, M. N. Hossain, M. A. Ali, M. A. Halim, *J. Biomol. Struct. Dyn.* **2021**, *39*, 3213–3224.

63. R. S. Joshi, S. S. Jagdale, S. B. Bansode, S. S. Shankar, M. B. Tellis, V. K. Pandya, A. Chugh, A. P. Giri, M. J. Kulkarni, *J. Biomol. Struct. Dyn.* **2021**, *39*, 1–16.

64. N. Lobo-Galo, M. Terrazas-López, A. Martínez-Martínez, Á. G. Díaz-Sánchez, *J. Biomol. Struct. Dyn.* **2021**, *39*, 3419–3427.

65. R. Garza-Lopez, J. Kozak, H. Gray, *ChemRxiv* **2020**, 1–13.

66. A. Böttcher, T. Takeuchi, K. I. Hardcastle, T. J. Meade, H. B. Gray, D. Cwikel, M. Kapon, Z. Dori, *Inorg. Chem.* **1997**, *36*, 2498–2504.

67. T. Takeuchi, A. Bottcher, C. M. Quezada, M. I. Simon, T. J. Meade, H. B. Gray, *J. Am. Chem. Soc.* **1998**, *120*, 8555–8556.

68. O. Blum, A. Haiek, D. Cwikel, Z. Dori, T. J. Meade, H. B. Gray, *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 6659–6662.

69. E. Toyota, K. K. S. Ng, H. Sekizaki, K. Itoh, K. Tanizawa, M. N. G. James, *J. Mol. Biol.* **2001**, *305*, 471–479.

70. W. Li, L. Jin, N. Zhu, X. Hou, F. Deng, H. Sun, *J. Am. Chem. Soc.* **2003**, *125*, 12408–12409.

71. N. Yang, J. A. Tanner, Z. Wang, J. D. Huang, B. J. Zheng, N. Zhu, H. Sun, *Chem. Commun.* **2007**, 4413–4415.

72. N. Yang, J. A. Tanner, B. J. Zheng, R. M. Watt, M. L. He, L. Y. Lu, J. Q. Jiang, K. T. Shum,

Y. P. Lin, K. L. Wong, M. C. M. Lin, H. F. Kung, H. Sun, J. D. Huang, *Angew. Chemie - Int. Ed.* **2007**, *46*, 6464–6468.

73. T. Shu, M. Huang, D. Wu, Y. Ren, X. Zhang, Y. Han, J. Mu, R. Wang, Y. Qiu, D. Y. Zhang, X. Zhou, *Virol. Sin.* **2020**, *35*, 321–329.

74. S. Yuan, R. Wang, J. F.-W. Chan, A. J. Zhang, T. Cheng, K. K.-H. Chik, Z.-W. Ye, S. Wang, A. C.-Y. Lee, L. Jin, H. Li, D.-Y. Jin, K.-Y. Yuen, H. Sun, *Nat. Microbiol.* **2020**, *5*, 1439–1448.

75. D. N. Frick, *Drug News Perspect.* **2003**, *16*, 355–362.

76. D. C. Wolf, C. H. Wolf, D. T. Rubin, *Am. J. Gastroenterol.* **2020**, *115*, 1298.

77. R. Wang, J. F.-W. Chan, S. Wang, H. Li, J. Zhao, T. K.-Y. Ip, Z. Zuo, K.-Y. Yuen, S. Yuan, H. Sun, *Chem. Sci.* **2022**, *13*, 2238–2248.

78. M. Aureliano, N. I. Gumerova, G. Sciortino, E. Garribba, A. Rompel, D. C. Crans, *Coord. Chem. Rev.* **2021**, *447*, 214143.

79. A. Bijelic, M. Aureliano, A. Rompel, *Chem. Commun.* **2018**, *54*, 1153–1169.

80. P. Yang, U. Kortz, *Acc. Chem. Res.* **2018**, *51*, 1599–1608.

81. N. V. Izarova, M. T. Pope, U. Kortz, *Angew. Chemie Int. Ed.* **2012**, *51*, 9492–9510.

82. J. T. Rhule, C. L. Hill, D. A. Judd, R. F. Schinazi, *Chem. Rev.* **1998**, *98*, 327–357.

83. M. B. Čolović, M. Lacković, J. Lalatović, A. S. Mougharbel, U. Kortz, D. Z. Krstić, *Curr. Med. Chem.* **2020**, *27*, 362–379.

84. J. Wang, Y. Liu, K. Xu, Y. Qi, J. Zhong, K. Zhang, J. Li, E. Wang, Z. Wu, Z. Kang, *ACS Appl. Mater. Interfaces* **2014**, *6*, 9785–9789.

85. S. G. Sarafianos, U. Kortz, M. T. Pope, M. J. Modak, *Biochem. J.* **1996**, *319*, 619–626.

86. R. Francese, A. Civra, M. Rittà, M. Donalisio, M. Argenziano, R. Cavalli, A. S. Mougharbel, U. Kortz, D. Lembo, *Antiviral Res.* **2019**, *163*, 29–33.

87. O. W. L. Carter, Y. Xu, P. J. Sadler, *RSC Adv.* **2021**, *11*, 1939–1951.

88. S. Xiu, A. Dick, H. Ju, S. Mirzaie, F. Abdi, S. Cocklin, P. Zhan, X. Liu, *J. Med. Chem.* **2020**, *63*, 12256–12274.

89. S. K. Nayak, *Mini Rev. Med. Chem.* **2021**, *21*, 689–703.

90. F. Li, *Annu. Rev. Virol.* **2016**, *3*, 237–261.

91. K. Al Adem, A. Shanti, C. Stefanini, S. Lee, *Pharmaceuticals* **2020**, *13*, 447.

92. J. Lan, J. Ge, J. Yu, S. Shan, H. Zhou, S. Fan, Q. Zhang, X. Shi, Q. Wang, L. Zhang, X. Wang, *Nature* **2020**, *581*, 215–220.

93. R. Cannalire, C. Cerchia, A. R. Beccari, F. S. Di Leva, V. Summa, *J. Med. Chem.* **2022**, *65*, 2716–2746.

94. B. K. Maiti, *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 1017–1019.

95. C. Gil, T. Ginex, I. Maestro, V. Nozal, L. Barrado-Gil, M. Á. Cuesta-Geijo, J. Urquiza, D. Ramírez, C. Alonso, N. E. Campillo, A. Martinez, *J. Med. Chem.* **2020**, *63*, 12359–12386.

96. K. Sargsyan, C. C. Lin, T. Chen, C. Grauffel, Y. P. Chen, W. Z. Yang, H. S. Yuan, C. Lim, *Chem. Sci.* **2020**, *11*, 9904–9909.

97. M. Aureliano, *BioChem* **2022**, *2*, 8–26.

98. D. Cirri, T. Marzo, I. Tolbatov, A. Marrone, F. Saladini, I. Vicenti, F. Dragoni, A. Boccuto, L. Messori, *Biomolecules* **2021**, *11*, 1858.

Figure legends

Figure 1. Chemical structures of the three worldwide-approved platinum drugs.

Figure 2. Chemical structures of some relevant inorganic drugs: **A**) Auranofin; B) Chloro(triethylphosphine)gold(I); **C**) Bismuth(III) potassium subcitrate; **D**) sodium stibogluconate; **E**) AS101 (Ammonium trichloro(dioxoethylene-O,O')tellurate); **F**) Mixture of 3-amino-4-hydroxyphenyl-As(III) compounds containing acyclic As_3 and As_5 species, known as Salvarsan; **G**) Titanocene dichloride; H) Boromycine; **I**) Tavaborole.

Figure 3. Representation of the SARS-CoV-2 cross-section with key proteins (top) and schematic pathway of SARS-CoV-2 viral life cycle. The initial attachment of SARS-CoV-2 to the host cells involves the binding of the viral S glycoprotein on the cellular receptor, ACE2 proteins. *Adapted from reference* [30] *under the terms of the Creative Commons Attribution License (CC BY).*

Figure 4. Structures of silver nitrate, silver sulfadiazine and Ag-3, as reported in ref. [58].

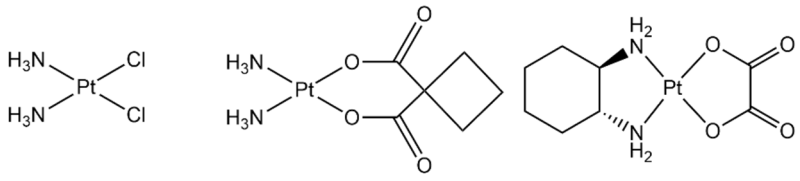
Figure 5. Molecular structures of $[Co(acacen)(NH_3)_2]Cl$ and [(meta-amidinosalicylidene-l-alaninato)copper(II)]Cl.

Figure 6. Molecular structures of some relevant Bi-based compounds studied as anti SARS-CoV-2 agents.

Figure 7. Some relevant examples for polyoxometalates compounds with biological activity. *Reproduced from reference* [58] *under the terms of the Creative Commons Attribution License (CC BY)*.

Figure 8. Structures of aurothiomalate (Au-2), Au-12, Au-33, Au-34.

Figure 1:



Cisplatin **Carboplatin** **Oxaliplatin**

Figure 2:

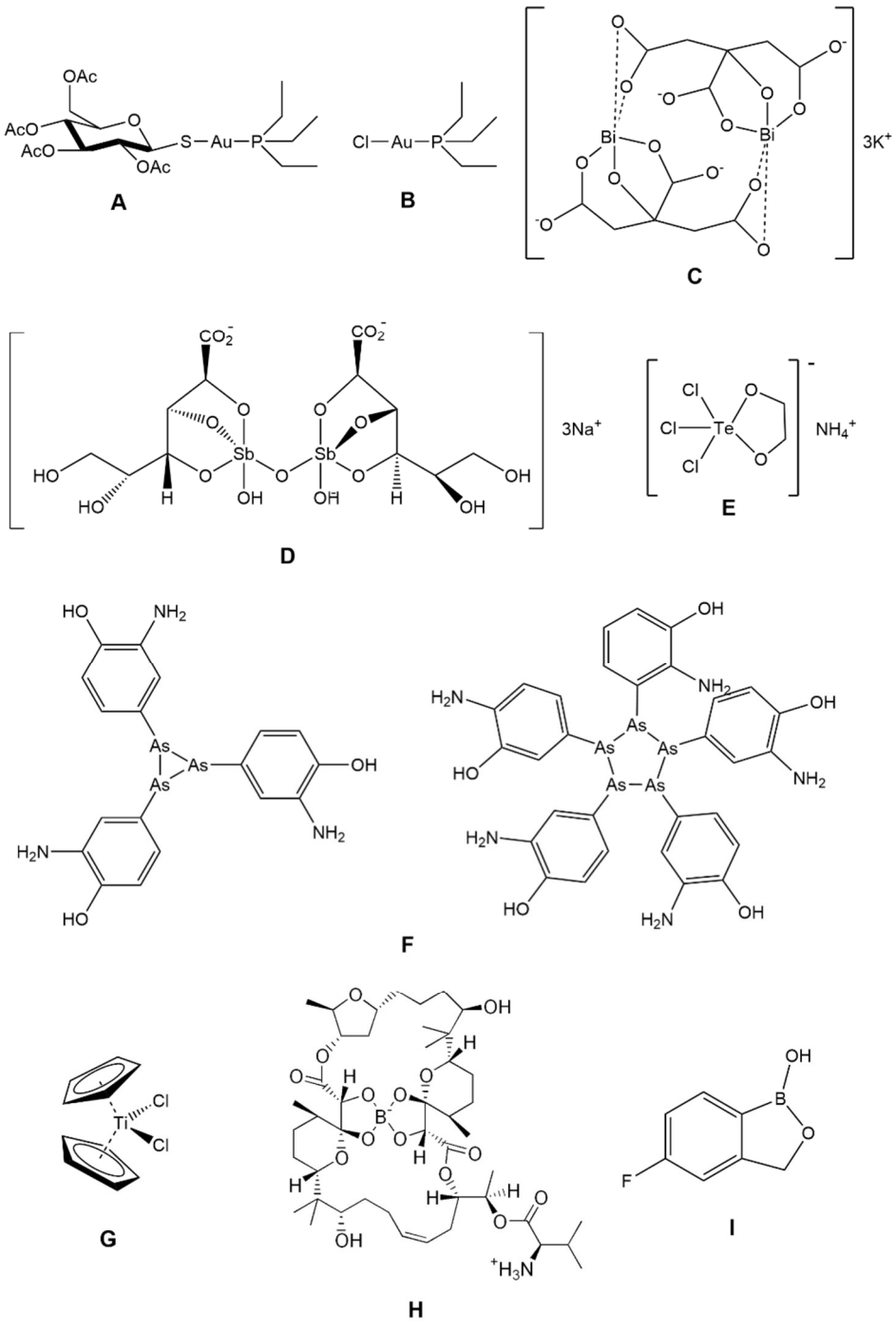


Figure 3:

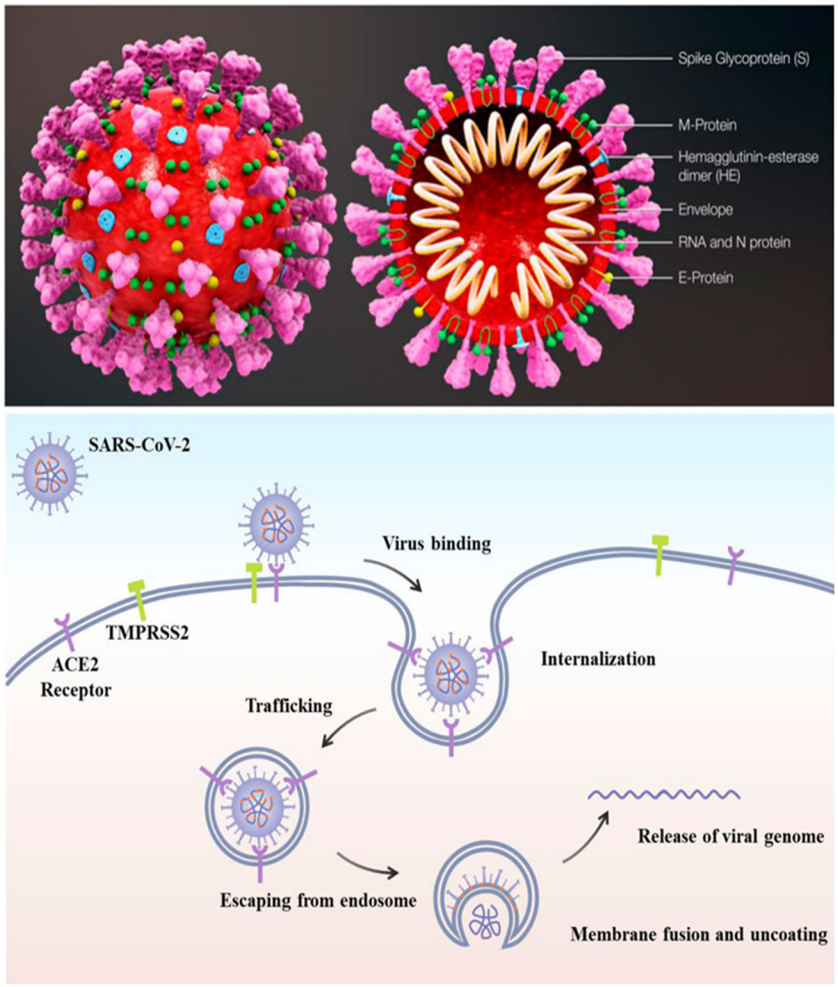
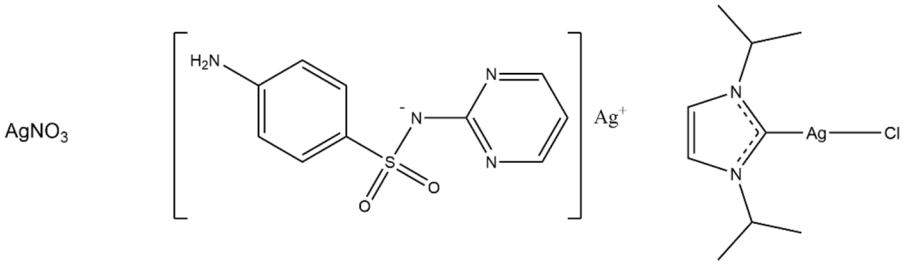
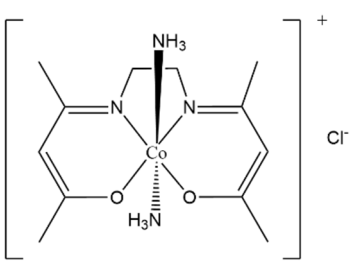

Spike Glycoprotein (S)
M-Protein
Hemagglutinin-esterase dimer (HE)
Envelope
RNA and N protein
E-Protein
SARS-CoV-2
Virus binding
TMPRSS2
ACE2
Receptor
Internalization
Trafficking
Release of viral genome
Escaping from endosome
Membrane fusion and uncoating

Figure 4:

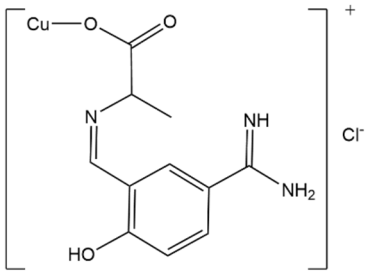


Silver Nitrate **Silver Sulfadiazine** **Ag-3**

Figure 5:

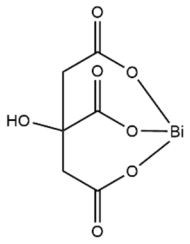


[Co(acacen)(NH_3)$_2$]Cl

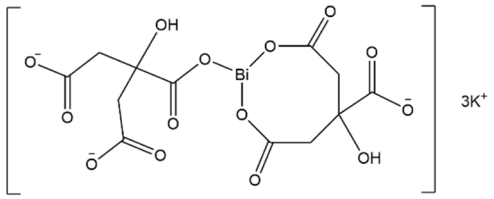


[(meta-amidinosalicylidene-l-alaninato)copper(II)]Cl

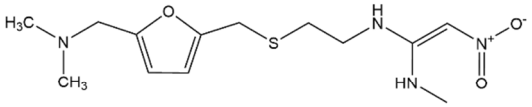
Figure 6:

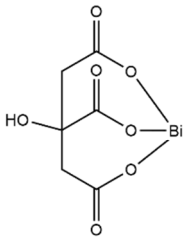


Bismuth citrate

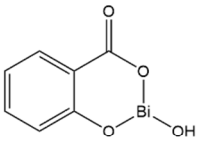


Bismuth potassium citrate

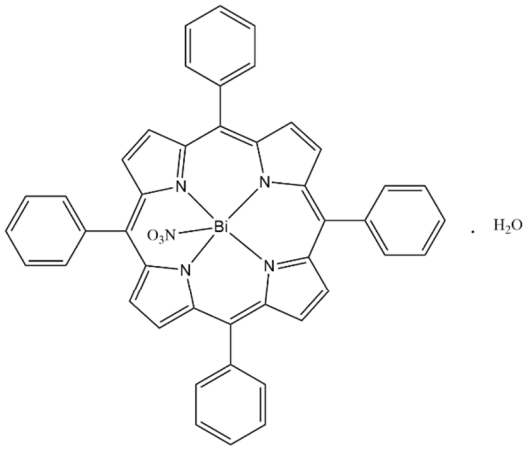




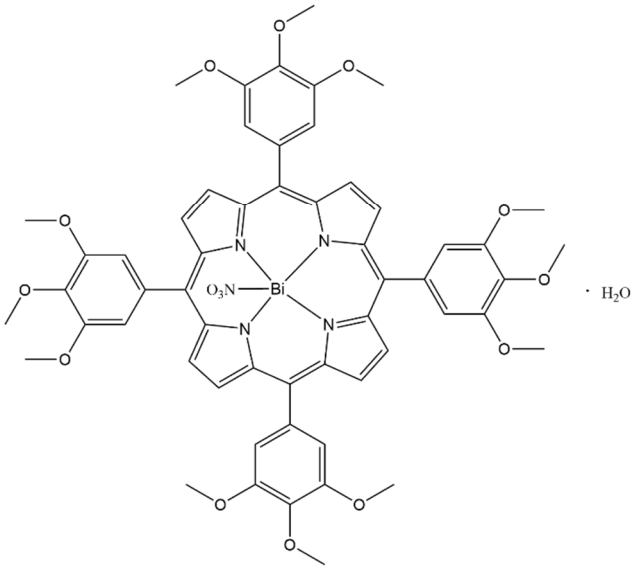
Ranitidine bismuth citrate



Bismuth subsalicylate



[Bi(5,10,15,20-tetraphenyl-21H,23H-porphine)(NO_3)]·H_2O



[Bi(5,10,15,20-tetra(1,2,3-trimethoxyphenyl)-21H,23H-porphine)(NO_3)]·H_2O

Figure 7:

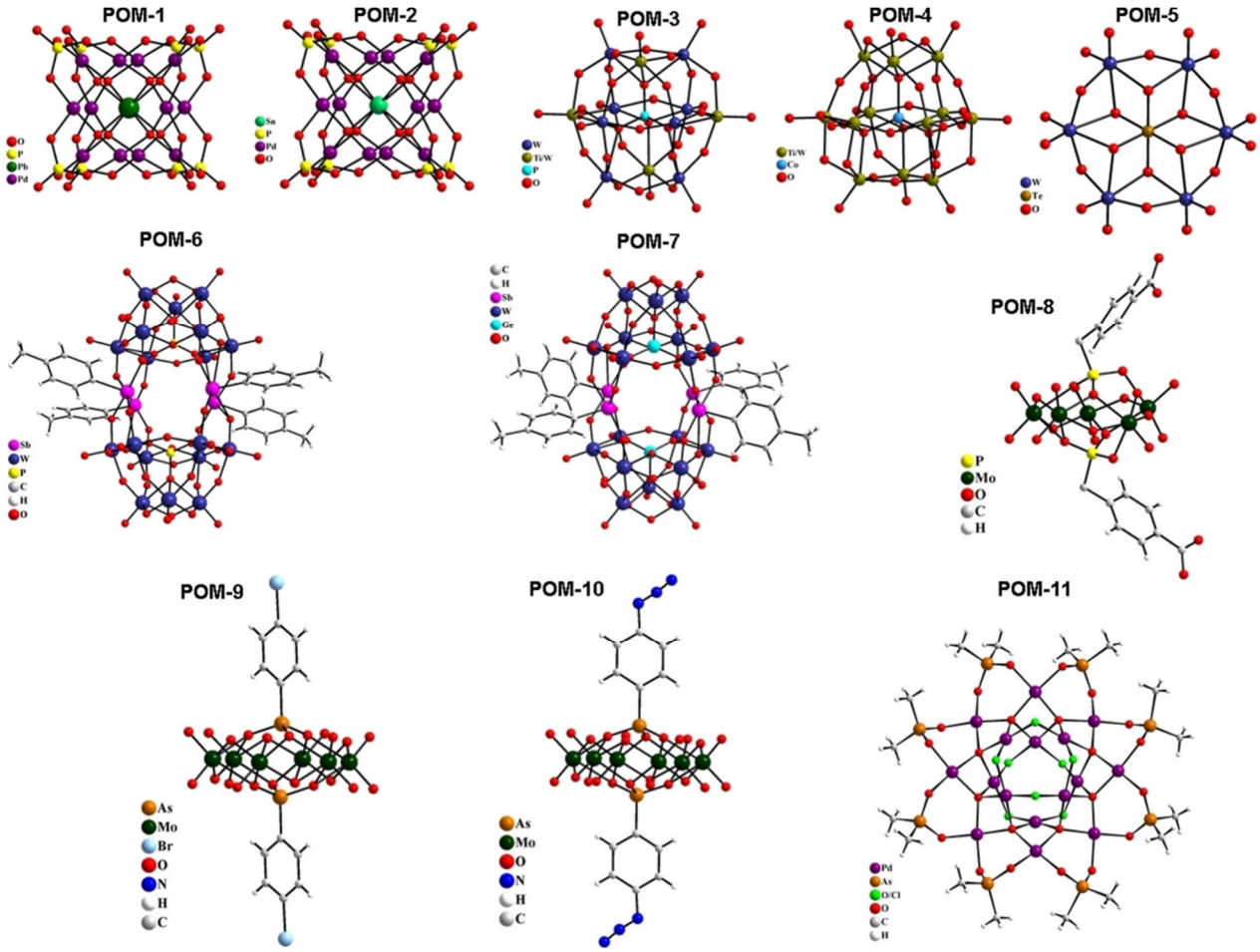
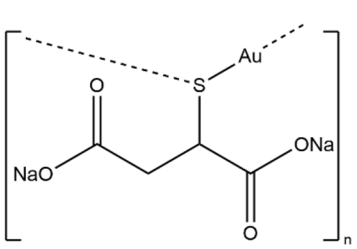
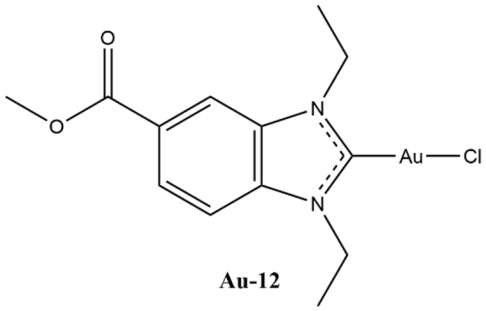


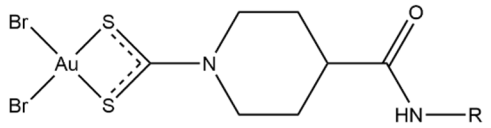
Figure 8:

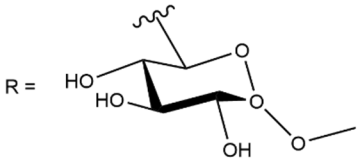


Aurothiomalate

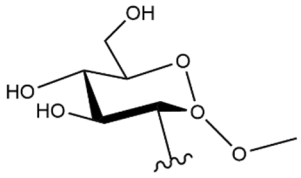


Au-12





Au-33



Au-34