Re\textsuperscript{1} Tricarbonyl Complexes as Coordinate Covalent Inhibitors for the SARS-CoV-2 Main Cysteine Protease

Johannes Karges, Mark Kalaj, Milan Gembicky, and Seth M. Cohen*

Abstract: Since its outbreak, the severe acute respiratory syndrome—coronavirus 2 (SARS-CoV-2) has impacted the quality of life and cost hundreds-of-thousands of lives worldwide. Based on its global spread and mortality, there is an urgent need for novel treatments which can combat this disease. To date, the 3-chymotrypsin-like protease (3CL\textsuperscript{pro}), which is also known as the main protease, is considered among the most important pharmacological targets. The vast majority of investigated 3CL\textsuperscript{pro} inhibitors are organic, non-covalent binders. Herein, the use of inorganic, coordinate covalent binders is proposed that can attenuate the activity of the protease. Re\textsuperscript{1} tricarbonyl complexes were identified that demonstrate coordinate covalent enzymatic inhibition of 3CL\textsuperscript{pro}. Preliminary studies indicate the selective inhibition of 3CL\textsuperscript{pro} over several human proteases. This study presents the first example of metal complexes as inhibitors for the 3CL\textsuperscript{pro} cysteine protease.

Introduction

Since its outbreak in December 2019 in Wuhan (Hubei, China), the severe acute respiratory syndrome—coronavirus 2 (SARS-CoV-2) has spread across the world. On 11\textsuperscript{th} March, the World Health Organization (WHO) officially declared this pulmonary disease as a global pandemic. To date, more than 96 million cases have been reported with more than 2 million confirmed deaths\cite{6} creating an urgent need for the development of novel therapeutics.

The papain-like protease (PL\textsuperscript{pro}) and the 3-chymotrypsin-like protease (3CL\textsuperscript{pro}), which is also known as the main protease, are considered among the most important viral targets for SARS-CoV-2. Clinical studies have indicated that infected patients treated with protease inhibitors have shown reduced symptoms and mortality\cite{2}. The PL\textsuperscript{pro} and 3CL\textsuperscript{pro} proteases are responsible for the processing of the viral polyproteins pp.1a and pp.1b that mediate functions required for viral replication and transcription and are crucial for viral maturation and infectivity\cite{18–24}. The inhibition of these proteases significantly disrupt the viral life cycle, presenting an important opportunity for therapeutic intervention\cite{18,19}. The compound disulfiram, which is approved for chronic alcohol dependence, has been reported to inhibit the PL\textsuperscript{pro} protease of SARS and is currently under investigation for SARS-CoV-2.\cite{3,4} Recently, the use of Au complexes as potential therapeutics has been reported, including as PL\textsuperscript{pro} inhibitors.\cite{5,6} As inhibitors of the 3CL\textsuperscript{pro} protease, the approved HIV therapeutics Lopinavir and Ritonavir are being studied in Phase III clinical trials for SARS-CoV-2.\cite{7} In addition, a number of other organic compounds are under consideration in preclinical trials as inhibitors of these proteases.\cite{8–10} Among these compounds, a handful of inhibitors have been identified that covalently bind to the catalytically active Cys145 amino acid.\cite{13–15} Despite these contributions, irreversible Michael acceptors such as Rupintrivir have failed in clinical trials due to their low bioavailability.\cite{16} in part due to reactions with off-target biological thiols. To address this limitation, the generation of reversible Cys-binding inhibitors has received increased attention in order to better target the Cys145 residue in the 3CL\textsuperscript{pro} protease active site.\cite{17}

Metal-based coordination compounds can exhibit sophisticated 3-dimensional (3D) shapes\cite{25–27} and can be designed to have selective reactivity, providing a pathway to develop covalent enzyme inhibitors.\cite{28,29} In this context, the use of 3D metal complexes as potential coordinate covalent inhibitors for the SARS-CoV-2 main protease 3CL\textsuperscript{pro} is presented. A [Re(2,2'-bipyridine)(CO)]\textsuperscript{+} fragment was identified that could bind to the catalytically active Cys145 amino acid through a metal-cysteine bond. The 2,2'-bipyridine ligand of the fragment was derivatized with various functional groups and chloride and water axial capping ligands were examined to develop a rudimentary structure–activity relationship (SAR). The resulting complexes were synthesized, characterized, and their in vitro activity investigated. To the best of our knowledge, these are the first metal complexes reported as inhibitors for the SARS-CoV-2 main protease 3CL\textsuperscript{pro}.

Results and Discussion

Rational Design

Previous studies by Fricker and co-workers demonstrated that Au\textsuperscript{III}, Pd\textsuperscript{II}, and Re\textsuperscript{V} complexes can inhibit the activity of the cysteine proteases Cathepsin B and K. These studies indicated that metal complexes can interact with catalytically active cysteine residues upon release of monodentate ligands to form coordinate covalent, but reversible, adducts.\cite{28,29} These studies provided the motivation to examine a variety of metal complexes for activity against 3CL\textsuperscript{pro}. Complexes of Pb, Bi, Te, Ni, Cu, Zn, Ru, Rh, Pd, Ag, Cd, Re, Pt, Au, and Hg were considered due to their high metal–sulfur bond enthalpy, especially in comparison to their metal-oxygen or metal-sulfur...
nitrogen bond enthalpy, which would be expected to produce high thiophilicity for Cys residues over other amino acid residues.\textsuperscript{[30,31]} Coordination compounds of these metals that were generally associated with poorer biological compatibility were removed from further consideration, resulting in compounds based on Ru, Rh, Pd, Re, Pt, or Au as possible options. Subsequently, known classes of compounds (Figure S1) possessing one vacant coordination site to allow for a metal–Cys bond were then modelled inside the active site pocket of 3CL\textsuperscript{pro}.

The molecular geometry of potential candidates (Figure S1) was determined using density-functional theory (DFT) calculations; each candidate possessed a chlorine atom as a placeholder for the enzyme coordination site. The geometry of the calculated structures was verified by comparison with crystal structures of structurally related compounds from the Cambridge Crystallographic Data Centre (CCDC). For docking experiments, the chlorine atom was removed to yield the “active” fragment for enzyme binding which was further considered as a rigid body. The metal complex was then docked to the Cys residues found in 3CL\textsuperscript{pro}. The enzyme possesses 12 Cys residues (Cys16, Cys22, Cys38, Cys44, Cys85, Cys117, Cys128, Cys145, Cys156, Cys160, Cys65, Cys300); however, the majority of these are buried inside the protein, with only three Cys (Cys85, Cys145, Cys156) surface accessible to fragments. After coordinating covalent docking of the complexes to these Cys residues, the binding pose was energetically minimized and scored using the GBVI/WSA dG force fields provided by MOE.

Among the modelled compounds, the fac-Re(CO)\textsubscript{3}(NN) (NN = bidentate nitrogen-donating ligand) fragment stood out as an attractive candidate (Table S1) that matched the protein architecture and could potentially react with the Cys145 active site residue (Figure 1, Figure S2). Among the docked binding poses, the fragment with the lowest energy was found to coordinate to Cys145 and not the other surface Cys residues. Previous studies have discussed the application of Re\textsuperscript{3} tricarbonyl as anticancer agents, luminescent probes, or radio-imaging agents, suggesting the biocompatibility of such compounds.\textsuperscript{[32–37]} Additional docking studies were performed with the scaffold that possessed symmetric substituents in all positions of the 2,2’-bipyridine ligand (vide infra). The docking pose of the Re\textsuperscript{3} tricarbonyl complexes functionalized with polar groups demonstrated opportunities to interact with the protein active site by hydrogen bonding and hydrophobic interactions. With these docking studies in hand, a series of complexes with either chloride or water as a labile ligand were synthesized, characterized, and evaluated as 3CL\textsuperscript{pro} inhibitors.

### Synthesis and Characterization

The synthesis of complexes 1, 3–7, 10–12, 17–18, 20, 22, 27, and 32 have been previously described (see Supporting Information for details), while 2, 8–9, 13–16, 19, 21, 23–26, 28–31, and 33–42 have not been previously reported (Figure 2). The functionalized 2,2’-bipyridine derivatives were prepared via literature procedures (see Supporting Information for details). The chloride capped Re\textsuperscript{3} tricarbonyl complexes 1–21 were synthesized by complexation of pentacarbonylchlororhenium with the corresponding 2,2’-bipyridine ligand. The aqua Re\textsuperscript{3} tricarbonyl complexes 22–42 were prepared by treatment of the chloride coordinated complex with silver trifluoromethanesulfonate, followed by precipitation upon addition of water. The aqua complexes were found to coordinate with silver trifluoromethanesulfonate, followed by precipitation upon addition of water. The water complexes were found to be stable in aqueous media.

**Figure 1.** Docking pose of the [Re(2,2’-bipyridine)(CO)\textsubscript{3}]\textsuperscript{+} fragment bound to the thiol of Cys145 in the active site of 3CL\textsuperscript{pro}.

**Figure 2.** Chemical structure of Re\textsuperscript{3} tricarbonyl complexes investigated in this study. The aqua coordinated complexes were isolated as triflate salts.
The interaction of the chloride (1) and aqua (22) Re¹ tricarbonyl complex with amino acids containing cationic (N₃₋₋p-tosyl-L-arginine methyl ester, L-histidine methyl ester, L-lysine methyl ester), anionic (N₃₋₋-tert-butoxy carbonyl-L-aspartic acid tert-butyler ester), polar (L-serine methyl ester, L-asparagine tert-butyler ester), and sulphur (L-cysteine methyl ester, L-methionine methyl ester) side chains was investigated (Figure 4) using equimolar amounts of metal complex and amino acid. Previous studies have indicated that Re¹ tricarbonyl complexes are able to react with Cys derivatives and a crystal structure has revealed that the Cys is covalently bound in axial position.

The stability of these compounds is an essential parameter for application as an enzyme inhibitor. Representative complexes 1 and 22 were incubated in water or phosphate buffered saline (PBS) at 37°C for 24 h in the dark and then analysed by HPLC. Compound 22 did not show any changes over the course of this experiment, while 1 showed slow hydrolysis of the chloride ligand, to yield complex 22 (Figures S9, S10). No other degradation products of these compounds were observed over this time period, suggesting that only the hydration of the chloride complex 1 needs to be considered in the context of the other experiments described herein.

Reactivity with Amino Acids

The tricarbonyl complexes 1 and 22 were incubated in water at 37°C with the corresponding amino acid for 24 h and analysed by HPLC. While 1 did not react with the majority of amino acids, it did react with L-cysteine methyl ester, presumably due to the high thiophilicity of the Re¹ centre. In contrast, 22 showed reactivity toward the acidic N₃₋₋-tert-butoxy carbonyl-L-aspartic acid tert-butyler ester and the basic L-histidine methyl ester amino acids, but did not achieve full conversion over 24 h. Notably, the incubation of 22 with L-cysteine methyl ester resulted in a single product peak with full conversion within 24 h. For additional insight into the kinetics of the capping group, the hydrolysis of the chloride ligand was investigated upon incubation of 1 in water and determination of the amount of hydrolysed product by HPLC in a time-dependent manner. Based on this experiment, the difference in reactivity between 1 and 22 can be explained by the slow hydrolysis rate of the chloride ligand in 1 with a value of 0.355 ± 0.051 × 10⁻³ s⁻¹. Following this evaluation, the crude product of the incubation of 22 with L-cysteine methyl ester was analysed by ESI-MS confirming the generation of [Re(2,2'-bipyridine)(L-cysteine methyl ester)(CO)]⁺ ([M+H]⁺ calcld for C₉₁H₁₅N₁₀O₁₂ReS: 562.0, found: 562.4). These results suggest that these compounds could serve as coordinate covalent inhibitors by binding to the catalytically active Cys145 in 3CLₐₚ.
with L-cysteine methyl ester was incubated with equimolar amounts of glutathione and GC376 to investigate if the metal complex was bound to the Cys adduct. While the native protein was found to have a deconvoluted mass of 33797 (Figure S13), upon incubation with GC376-protein covalent adduct (m/z 34225). The bound thiol was exchanged in both cases, showing the reversibility of this reaction (Figure S15). Incubation of 3CLpro with GC376, followed by incubation with 22 resulted in only the formation of the GC376-protein covalent adduct (m/z 34201), with no mixture of adducts and no addition of the Re³ tricarbonyl complex (Figure S16). These results strongly suggest that 22 is targetting the same residue as GC376, namely active site Cys145.

Following this initial assessment, the inhibition activity against the SARS-CoV-2 3CLpro was investigated. The 3CLpro protease was pre-incubated with Re³ compounds and enzyme inhibition was monitored by conversion of a non-fluorescent substrate to a fluorescent product (see Supporting Information for details). Compounds 1–42 were screened against 3CLpro at a concentration of 200 μM (Figure 5). As expected, due to the slow release of the chloride atom, compounds 1–21 did not show significant inhibition activity. In contrast, all aqua compounds 22–42 were able to inhibit the activity of the protease, with remaining enzymatic activity reduced to ≈20–
The inhibition by the lead structures was quantified by determination of their IC\textsubscript{50} values (Table 1). The complexes displayed IC\textsubscript{50} values between 7.5–24.1 μM (Figure S17). The carboxylic acid functionalized compounds (33, 38) have the highest IC\textsubscript{50} values while the amine functionalized compounds (34, 39) have the lowest IC\textsubscript{50} values. This could be the result of these functional groups being directed at negatively charged surfaces inside the enzyme active site (Figure S18). Based on this hypothesis, the carboxylic acids on the Re\textsuperscript{I} tricarbonyl complex would result in a repulsion with the protein surface, while the amine substituents would present attractive interactions, resulting in the observed differences in inhibition activity. Although only a preliminary SAR, the observation that preferred substitution patterns and functional groups on the bipyridine group can be identified suggests that more selective and active Re\textsuperscript{I} compounds can be designed for inhibition of 3CL\textsuperscript{pro}. Overall, 34 was identified as having the highest inhibitory effect and was therefore studied further.

Table 1: Summary of the binding data of selected compounds against 3CL\textsuperscript{pro}. Values and standard deviations are derived from three independent experiments.

| Compound | IC\textsubscript{50} [μM] |
|----------|-----------------------|
| 22       | 13.8 ± 2.1            |
| 31       | 12.8 ± 1.9            |
| 32       | 15.7 ± 1.4            |
| 33       | 24.1 ± 1.2            |
| 34       | 7.5 ± 1.3             |
| 37       | 13.5 ± 2.3            |
| 38       | 21.1 ± 2.7            |
| 39       | 9.6 ± 1.3             |
lowest IC\textsubscript{50} value at 7.5 ± 1.3 μM. To ensure that the intact coordination compound 34 is responsible for the inhibitory effect, the ligand 4,4’-diamino-2,2’-bipyridine and the metal complex pentacarbonylchlororhenium were screened against 3CL\textsubscript{pro}. Both components showed no activity (IC\textsubscript{50} value > 100 μM), confirming that 34 is the active species.

As glutathione and other biologically present thiols in cells could influence the activity of these compounds, the activity of the Cys 43 and glutathione 44 functionalized derivatives towards 3CL\textsubscript{pro} was tested. The complexes were found to display slightly mitigated activity compared to many of the other complexes (43, IC\textsubscript{50} = 20.8 ± 3.6 μM; 44, IC\textsubscript{50} = 26.7 ± 4.1 μM). A hallmark of covalent inhibitors is time-dependent inhibition, therefore, 1 (axial Cl), 22 (axial H\textsubscript{2}O), 43 (axial Cys), and 44 (axial glutathione) derivatives (at a concentration of 20 μM) were pre-incubated with 3CL\textsubscript{pro} for various time periods (30, 60, 120, and 240 min) and the remaining enzyme activity was measured (Figure S19). While 1 demonstrated no inhibition and 22 showed near complete inhibition over this time period, 43 and 44 showed a gradual reduction of 3CL\textsubscript{pro} activity as a function of time. Within 240 min, 43 and 44 had reduced enzymatic activity to the same level as compound 22, indicating that these axial thiols can be exchanged, acting as reversible, coordinate covalent inhibitors. Such thiol substituted Re\textsuperscript{3+} tricarbonyl complexes could even serve as a type of prodrug for this class of coordinate covalent inhibitors. To further examine the effect of glutathione on inhibitory activity, an enzyme inhibition assay with compound 34 was performed with a 30 min pre-incubation with 1 mM glutathione (which is comparable to levels of biological thiols), followed by a 30 min incubation with 3CL\textsubscript{pro}. As expected, the activity of the 34 was reduced, possessing an IC\textsubscript{50} value of 13.6 ± 2.8 μM; however, this represents only 2-fold loss of activity. Following this, 34 was again pre-incubated for 30 min with 1 mM glutathione followed by a 240 min incubation with 3CL\textsubscript{pro}. Interestingly, the inhibition by compound 34 with this extended incubation time showed an IC\textsubscript{50} value of 9.1 ± 1.8 μM, which is only slightly changed in comparison to the standard assay without addition of glutathione (Table 1). By comparison, the activity of the anticancer drug cisplatin is also reduced in the presence of glutathione,[52] and hence the reduced reactivity here is both expected and not an insurmountable impediment to further drug development.

Compound 34 was further investigated using a thermal shift assay as an orthogonal technique for evidence of enzyme binding. Compound 34 was incubated with 3CL\textsubscript{pro} for 30 min at 37°C and the melting temperature of the enzyme measured. While 4,4’-diamino-2,2’-bipyridine and the metal complex pentacarbonylchlororhenium showed only a negligible effect (ΔT = 0.2 ± 0.4), incubation with 34 gave a slight increase in the melting temperature of 3CL\textsubscript{pro} (ΔT = 2.4 ± 0.6), indicative of inhibitor binding. Interestingly, the change in melting temperature was found to be in the same range as for the known inhibitor GC376 (ΔT = 3.1 ± 0.5).[53] The binding to 3CL\textsubscript{pro} was further investigated by UV/Vis absorption spectroscopy (Figure S20). Compound 34 and 3CL\textsubscript{pro} were combined and their absorption properties monitored every 2 min for 120 min. While no changes in the absorption spectra for 34 and 3CL\textsubscript{pro} alone were observed under these conditions, the combined mixture of both showed changes. Within 30 min, an asymptotic absorption pattern was reached which showed no further changes after 60 min, suggestive of inhibitor binding (Figure S20).

As a means to characterize the binding affinity of the metal complex to the enzyme independently of intermediates, the ratio of the second reaction rate constant (k\textsubscript{2}) in dependence of inhibition constant (K\textsubscript{i}) was determined according to previously published procedures.[54] Lead compound 34 was incubated with 3CL\textsubscript{pro} and the activity of the enzyme was monitored in a time-dependent manner. The metal complex was found to slowly bind to 3CL\textsubscript{pro} with a ratio of k\textsubscript{i}/K\textsubscript{i} of 174 M\textsuperscript{-1} s\textsuperscript{-1}, which is two orders of magnitudes slower than the organic, covalent inhibitor GC376.[54] GC376 is a more potent inhibitor (IC\textsubscript{50} = 0.19 ± 0.04 μM) than 34, which is consistent with differences in aforementioned k\textsubscript{i}/K\textsubscript{i} values. In addition, as found with compound 22, incubation of compound 34 with 3CL\textsubscript{pro} produced in an adduct that could be identified by mass spectrometry (see above). As expected, the deconvoluted mass peak of 3CL\textsubscript{pro} shifted to 34255 (Figure S21) corresponding to a single attached Re\textsuperscript{3+} tricarbonyl complex 34 (m/z 457).

Covalent 3CL\textsubscript{pro} inhibitors could also bind and inhibit cathepsins, especially cathepsin B, resulting in undesired side reactions and off-target effects.[55] Inhibition of cathepsins is particularly relevant because they are found in the respiratory system, where SARS-CoV-2 would infect.[56] To investigate this potential shortcoming, cathepsin B was incubated with 34 for 2 h followed by analysis by mass spectrometry. While matrix-assisted laser ionization-time of flight mass spectrometry (MALDI-TOF-MS) identified the covalent adduct of 34 with 3CL\textsubscript{pro} (Figure S22), no adduct formation was observed between 34 and cathepsin B (Figure S23), indicative of some selectivity of 34 towards 3CL\textsubscript{pro} over this cysteine protease. To further evaluate selectivity, the activity of 34 against the human serine protease dipetidyl peptidase-4 (DPP4), the aspartate protease beta-secretase 1 (BACE1) and cysteine protease cathepsin B was measured in an inhibition assay (Figure 6). Encouragingly, compound 34 did not show meas-
urable activity (IC\textsubscript{50} value > 100 μM) towards DPP4 and cathepsin B, and showed only weak inhibition of BACE1 (IC\textsubscript{50} value = 89.2 ± 5.7 μM). These preliminary studies indicate that selective inhibition of 3CL\textsuperscript{pro} can be achieved over several human proteases.

Conclusion

In summary, the synthesis and biophysical evaluation of Re\textsuperscript{1} tricarbonyl complexes as inhibitors of the SARS-CoV-2 main protease 3CL\textsuperscript{pro} has been achieved. A series of Re\textsuperscript{1} complexes with chloride and water as capping ligands and differently substituted 2,2′-bipyridine ligands were prepared. While the coordinated chloride was only slowly released, the aqua complex 22 showed reactivity towards amino acids within one hour. Mass spectrometry experiments verified the coordinate covalent binding of a single Re\textsuperscript{1} tricarbonyl complex to 3CL\textsuperscript{pro}. Using an enzymatic assay against 3CL\textsuperscript{pro}, several complexes were found to be active, with IC\textsubscript{50} values of < 10 μM. Preliminary investigations show selectivity against human proteases. These results suggest that Re\textsuperscript{1} tricarbonyl complexes can serve as a starting scaffold for the development of potent, selective SARS-CoV-2 inhibitors.

Acknowledgements

The authors acknowledge the help of Ryjul W. Stokes with the measurement of NMR spectra and Dr. Yongxuan Su (UCSD, Molecular Mass Spectrometry Facility) with mass spectrometry. M.K. is supported by the Department of Defense (DoD) through the National Defense Science and Engineering Graduate (NDSEG) Fellowship Program is the recipient of an Achievement Rewards for College Scientists (ARCS) Foundation Fellowship. This work was supported by a grant from the National Institutes of Health (R21 AI138934).

Conflict of interest

The authors declare no conflict of interest.

Keywords: antiviral agents · bioinorganic chemistry · medicinal inorganic chemistry · protease inhibitor · SARS-CoV-2

[1] https://coronavirus.jhu.edu/map.html, last accessed 20.01.2021.
[2] C. M. Chu, V. C. C. Cheng, I. F. N. Hung, M. M. L. Wong, K. H. Chan, K. S. Chan, R. Y. T. Kao, L. M. Poon, C. L. P. Wong, Y. Guan, J. S. M. Peiris, K. Y. Yuen, Thorax 2004, 59, 252 – 256.
[3] I. L. Lu, N. Mahindroo, P.-H. Liang, Y.-H. Peng, C.-J. Kao, K.-C. Tsai, H.-P. Hsieh, Y.-S. Chao, S.-Y. Wu, J. Med. Chem. 2006, 49, 5154 – 5161.
[4] A. E. Gorbalenya, A. P. Donchenko, V. M. Blinov, E. V. Koonin, FEBS Lett. 1989, 243, 103 – 114.
[5] Y. Chen, Q. Liu, D. Guo, J. Med. Virol. 2020, 92, 418 – 423.
[6] M.-H. Lin, D. C. Moses, C.-H. Hsieh, S.-C. Cheng, Y.-H. Chen, C.-Y. Sun, C.-Y. Chou, Antiviral Res. 2018, 150, 155 – 163.
[32] S. C. Marker, A. P. King, S. Granja, B. Vaughan, J. J. Woods, E. Boros, J. J. Wilson, Inorg. Chem. 2020, 59, 10285–10303.
[33] C. C. Konkankit, A. P. King, K. M. Knopf, T. L. Southard, J. J. Wilson, ACS Med. Chem. Lett. 2019, 10, 822–827.
[34] C. Philippe, D. Didier, V. Veenen, Curr. Pharm. Des. 2019, 25, 3306–3322.
[35] M. S. Capper, H. Packman, M. Rehkämper, ChemBioChem 2020, 21, 2111–2115.
[36] L. J. Rasreja, D. Siegmund, A. L. Cordes, J. Gildenhaupt, K. Gerwert, S. Hahn, N. Metzler-Nolte, Chem. Commun. 2017, 53, 905–908.
[37] M. Muñoz-Osses, F. Godoy, A. Fierro, A. Gómez, N. Metzler-Nolte, Dalton Trans. 2018, 47, 1233–1242.
[38] P. Kurz, B. Probst, B. Spingler, R. Alberto, Eur. J. Inorg. Chem. 2006, 2966–2974.
[39] M. Towrie, A. W. Parker, K. L. Ronayne, K. F. Bowes, J. M. Cole, P. R. Raithby, J. E. Warren, Appl. Spectrosc. 2009, 63, 57–65.
[40] J. M. Smieja, C. P. Kubiak, Inorg. Chem. 2010, 49, 9283–9289.
[41] B. J. Coe, S. P. Foxon, R. A. Pilkington, S. Sánchez, D. Whittaker, K. Clays, N. Van Steerteghem, B. S. Brunschwig, Organometallics 2016, 35, 3014–3024.
[42] M. L. Clark, B. Rudshytein, A. Ge, S. A. Chabolla, C. W. Machan, B. T. Pcski, J. Song, G. Canzi, T. Lian, V. S. Batista, C. P. Kubiak, J. Phys. Chem. C 2016, 120, 1657–1665.
[43] G. F. Manbeck, J. T. Muckerman, D. J. Szalda, Y. Himeda, E. Fujita, J. Phys. Chem. B 2015, 119, 7457–7466.
[44] G. A. Bhat, A. Z. Rashad, T. M. Folsom, D. J. Darensbourg, Organometallics 2020, 39, 1612–1618.
[45] D. A. Popov, J. M. Luna, N. M. Orchanian, R. Haiges, C. A. Downes, S. C. Marinescu, Dalton Trans. 2018, 47, 17450–17460.
[46] S. Lense, N. A. Piro, S. W. Kassel, A. Wildish, B. Jeffery, Acta Crystallogr. Sect. E 2016, 72, 1201–1205.
[47] K. M. Knopf, B. L. Murphy, S. N. MacMillan, J. M. Baskin, M. P. Barr, E. Boros, J. J. Wilson, J. Am. Chem. Soc. 2017, 139, 14302–14314.
[48] S. Keller, Y. C. Ong, Y. Lin, K. Cariou, G. Gasser, J. Organomet. Chem. 2020, 906, 121059.
[49] M. S. Capper, A. Enríquez García, N. Macia, B. Lai, J.-B. Lin, M. Nomura, A. Alìhosseinzadeh, S. Ponnurangam, B. Heyne, C. S. Schmanko, F. Julievich, J. Biol. Inorg. Chem. 2020, 25, 759–776.
[50] J. Lecina, Ó. Palacios, S. Attrian, M. Capdevila, J. Saades, J. Biol. Inorg. Chem. 2015, 20, 465–474.
[51] T. R. Steel, C. G. Hartinger, Metallomics 2020, 12, 1627–1636.
[52] H. H. W. Chen, M. T. Kuo, Met.-Based Drugs 2010, 2010, 430939.
[53] Y. Kim, H. Liu, A. C. Galasiti Kankanamalage, S. Weerasekara, D. H. Hua, W. C. Groutas, K.-O. Chang, N. C. Pedersen, PLOS Pathog. 2016, 12, e1005531.
[54] C. Ma, M. D. Sacco, B. Hurst, J. A. Townsend, Y. Hu, T. Szeto, X. Zhang, B. Tarbet, M. T. Marty, Y. Chen, J. Wang, Cell Res. 2020, 30, 676–692.
[55] K. Steuten, H. Kim, J. C. Widen, B. M. Babin, O. Onguka, S. Lovell, O. Bølgi, B. Cerikan, M. Cortese, R. K. Mair, J. M. Bennett, R. Geiss-Friedlander, C. Peters, R. Bartenschlager, M. Bogyo, BioRxiv 2020, https://doi.org/10.1101/2020.11.21.392753.
[56] S. Lukassen, R. L. Chua, T. Trefzer, N. C. Kahn, M. A. Schneider, T. Muley, H. Winter, M. Meister, C. Veith, A. W. Boots, B. P. Hennig, M. Kreuter, C. Conrad, R. Eils, EMBO J. 2020, 39, e105114.
[57] Deposition Numbers 2026146, 2026147, 2026148, 2026149, 2026150, 2026151, 2026152, 2026153, 2026154, 2026155, 2026156 and 2026157 (for 3, 7, 8, 11, 13, 14, 15, 19, 20, 22, 37, and 42, respectively) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: December 17, 2020
Revised manuscript received: February 10, 2021
Accepted manuscript online: February 19, 2021
Version of record online: March 26, 2021