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 Modeling of Re(I) tricarbonyl complexes against SARS-CoV-2 receptor via DFT, *in-silico* molecular docking, and QSAR

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Abstract

The quest for potential antiviral drug for the ongoing SARS-CoV-2 pandemic has posed a serious challenge to the scientific community. While several potential drugs have been proposed from organic molecular perspective, the uses of 3D metal complexes of bipyridine ligand have been recently proven to be potential coordinate covalent inhibitors for the SARS-CoV-2 main 3-Chymotrypsin-like protease (3CLPro). Herein, we present detailed DFT studies, *in silico* molecular docking, and multilinear regression analysis (MLRA) investigations of eight (8) selected biologically active Rhenium Tricarbonyl complexes designed and modeled based on the results of Karges and co-workers. The atomistic DFT modeling was conducted to investigate the reactivity, structural stability, and electronic properties based on frontier molecular orbitals (FMO), natural bond orbitals (NBO), interaction energies, density of states (DOS), charge distributions, and molecular thermochemical parameters. Molecular docking simulations were performed to study the binding interactions between the selected biologically active complexes and the target SARS-CoV-2 viral protein, 3CLPro. The best quantitative structure-activity relationship (QSAR) was established to demonstrate the correlations between the DFT calculated descriptors and the *in vitro* biological activities (IC₅₀) of structures.

1. Introduction

Bioinorganic chemistry deals with the experimental and theoretical investigation of metal complexes in living systems. For decades, the coordination chemistry of bipyridine based ligands has been the subject of great interest. This ligands base has been used in the areas of photovoltaic cell, electrocatalysts for hydrogen evolution reaction, carbon dioxide reduction into hydrocarbon fuel, bioorganic medicine, and coordination compounds of biologically active ligands.

Density functional theory (DFT) and *in silico* Molecular docking has become increasingly viable tools for the computational investigation of metal complexes in order to validate the 3D Stereochemical structure of the complexes along with predicting the possible application in biological systems. Gaur et al., in 2017 carried out investigation of nitrato bridged dinuclear complexes of bipyridine-type ligands using a battery of physicochemical techniques, X-ray crystallography, and DFT studies [11]. Here, the computed vibrational analysis, electronic absorption spectrum, electronic properties, molecular electrostatic potential, natural bond orbitals analysis and other structural parameters were investigated using the DFT/B3LYP/6–31 G (d, p) computational methods. Gaur et al., in 2017 carried out investigation of nitrato bridged dinuclear complexes of bipyridine-type ligands using a battery of physicochemical techniques, X-ray crystallography, and DFT studies [12]. Their elucidated structures and the associated UV-visible absorption spectra were

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https://doi.org/10.1016/j.chphi.2022.100105
Received 27 June 2022; Received in revised form 16 August 2022; Accepted 23 August 2022
Available online 24 August 2022
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supported computationally using density functional theory (DFT) and TD-DFT theoretical approaches.

Herein, we present detailed DFT studies, in silico molecular docking, and Multilinear regression analysis (MLRA) investigations of eight (8) selected Rhenium Tricarbonyl complexes which were reported by Karges et al., [Angew. Chem. Int. Ed., 2021] and have been experimentally tested to have good inhibitory activity (IC50) against SARS-CoV-2 main receptor [13]. Density functional theory studies were conducted to investigate the HOMO-LUMO energies, second order perturbation energy from natural bond orbital (NBO) analysis, charge distribution using Mulliken analysis, intramolecular metal complex interaction energy analysis, and topological studies using quantum theory of atoms-in-molecules (QTAIM) were evaluated. Molecular docking was conducted to investigate the interaction between the complexes (ligands) and the target receptor protein (3CLpro) in order to elucidate the number of H-bonds, distance, and binding affinity of the ligand. Finally, quantitative structure activity relationship (QSAR) using multilinear regression analysis (MLRA) method was applied in order to correlate the DFT calculated descriptors with the in vitro biological activity (IC50) of the complexes against the SARS-CoV-2 cysteine protein.

2. Computational methods

2.1. DFT methods

2.1.1. Modeling and geometry optimization

Geometry optimization of the studied complexes were performed using B3LYP which includes Becke’s (B3) Parameter exchange functional along with Lee, Yang Parr’s (LYP) gradient corrected correlation functional [14,15] using Gaussian 09 and GaussView 6.0 softwares [16, 17]. Pre-geometry optimization using the molecular mechanic optimization with MM + force field implemented in the HyperChem program [18] has been performed on model structures and outputs used for further geometry optimization using a general basis set of 6–31+G(d) for the H, C, N, O atoms, and the LanL2DZ basis set for Re atom. Natural bond orbital (NBO) analyses were calculated by the NBO 3.1 module embedded in Gaussian. The quantum theory of atoms-in-molecules (QTAIM) investigations and all other wavefunction analyses were conducted by Multiwfn 3.7 dev, which is a multifunctional wavefunction program [19]. Unless otherwise specified, the default settings were used throughout our calculations. All molecular electrostatic (MESP) isosurface maps were rendered by visual molecular dynamic (VMD) 1.9.3 program [20] based on the outputs of Multiwfn analyzer.

2.1.2. Quantum chemical calculations

The quantum chemical calculations were conducted to calculate the global reactivity electronic descriptors based on the well-known Koopman’s approximation [21]. According to the approximation, the ionization potential and the electron affinity are approximately equal to the negative of the HOMO and LUMO energies respectively.

\[
\text{IP} = -E_{\text{HOMO}} \\
\text{EA} = -E_{\text{LUMO}}
\]

Hence, the global reactivity descriptors could be computed using Eqs. (3)–(6) as suggested in literatures [22].

\[
-\mu = 1/2(E_{\text{HOMO}} + E_{\text{LUMO}}) = \chi
\]

\[
\eta = 1/2(IP - EA) = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2}
\]

\[
\omega = \frac{\mu^2}{2\eta}
\]

\[
S = \frac{1}{2\eta} = \frac{1}{IP - EA} = \frac{1}{E_{\text{LUMO}} - E_{\text{HOMO}}}
\]

Where \(\mu\), \(\chi\), \(\eta\), \(\omega\), and \(S\) are the chemical potential, electronegativity, chemical hardness, electrophilicity, and chemical softness respectively.

2.1.3. Natural bond orbital (NBO) calculations

The NBO calculation is based on the second-order perturbation Fock matrix used to study the Lewis valence orbital (donor) and non-Lewis valence orbital (acceptor) interactions in the NBO basis [23,24]. The stabilization energy associated with the electron delocalization between Lewis (filled) and non-Lewis (unfilled) orbital is estimated as.

\[
E^{(2)} = \Delta E_{\text{int}} = -q_i F^2(i,j) \varepsilon_{ij}
\]

Where \(q_i\) is the donor orbital occupancy, \(\varepsilon_{ij}\) and \(\varepsilon_j\) are the diagonal elements, and \(F_{ij}\) is the Fock matrix element.

2.1.4. Complex interaction energy calculations

The interaction energy between the constituent species: bipyridine, water, rhenium, and carbonyl molecules that make up the complex is calculated according to the counterpoise procedure (CP) proposed by Boys and Bernardi [25] based on the equation.

\[
E_{\text{int}}(ABCD) = E_{\text{ABC}}(ABCD) - E_{\text{ABC}}(A) - E_{\text{ABC}}(B) - E_{\text{ABC}}(C) - E_{\text{ABC}}(D)
\]

Where \(E_{\text{int}}(ABCD), E_{\text{ABC}}(ABCD), E_{\text{ABC}}(A), E_{\text{ABC}}(B), E_{\text{ABC}}(C), \) and \(E_{\text{ABC}}(D)\) refers to the total energy of the complex, energy of monomer A, energy of monomer B, energy of monomer C, and energy of monomer D present in the complex respectively.

2.1.5. Aromaticity indices calculations

The aromaticity indices were measured by one of the most popular indexes called HOMA which was proposed by Ref. [26] and the general form was given by [27] to estimate the aromaticity of the rings. The acceptable general form is defined as

\[
\text{HOMA} = 1 - \frac{\sum_{i,j}(R_{\text{ref}} - R_{ij})^2}{N}
\]

Where \(N\) is the total number of atoms considered, \(j\) denotes the atom next to atoms \(i\), \(\alpha\), and \(R_{\text{ref}}\) are pre-calculated constants.

2.1.6. Molecular electrostatic potential (MESP) calculations

The MESP is important in studying the interaction between hydrogen bonding and the distribution of charge in a molecule. For the studied compound, titled structure the MEP was calculated using the equation [28,29].

\[
V(r) = \sum Z_i/(R_i - r) - \int \rho(r’)/(r’ - r)dr’
\]

Where the summation runs over all the nuclei A in the compound, \(Z_i\) is the charge of the nucleus \(A\) located at \(R_i\) and \(\rho(r)\) is the electron density function of the molecule.

2.1.7. Thermodynamics

The optimized Gaussian output files were used for the thermodynamic DFT calculations by selecting frequency as the job type while the various molecular thermochemical properties were computed using Shermo2.0.4 code which is a general program for calculating molecular thermodynamic parameters developed by Tian Lu [30]. All the calculations for enthalpy and free energy of the reactions were done using the data obtained from the optimized structures adopting the following equations according to [31].
\[ \Delta H(298K) = \sum_{\text{Product}} (e_0 + H_{\text{corr}}) - \sum_{\text{Reactant}} (e_0 + H_{\text{corr}}) \]  
(11)

\[ \Delta G(298) = \sum_{\text{Product}} (e_0 + G_{\text{corr}}) - \sum_{\text{Reactant}} (e_0 + G_{\text{corr}}) \]  
(12)

\( e_0 \) is the electronic energy while \( H_{\text{corr}} \) is the total energy and thermal correction to \( H \).

2.2. Molecular docking simulation

2.2.1. Protein selection/preparation

The 3D structures of the SARS-CoV-2 cysteine protease which is 3-Chymotrypsin-like protease (3CL\textsuperscript{PRO}) was downloaded from the Protein Data Bank (www.RSCPDB.org) and prepared using protein preparation module of Molegro Virtual Docker (MVD) package 6.0 [32], the MVD module is able to assign missing bonds, bond order, flexible torsions, create explicit hydrogen’s and charges to the protein molecule and makes them suitable for docking procedure. The ligands (complexes) used for docking were subjected to pre-geometry optimization using the molecular mechanic optimization with MM + force field implemented in the HyperChem program [18] has been performed on model structures and outputs used for the molecular docking. The crystal structure of SARS-CoV-2 3CL\textsuperscript{PRO} (PDB: 6Y2F) main protease is displayed in Fig. 1.

2.2.2. Molecular docking protocol

Molecular docking is used to estimate the binding energy of protein-ligand interaction and identify the plausible ligand binding sites. The docking analysis was conducted with Molegro Virtual Docker (DMV) package. During the docking process, create surface module of MVD was invoked to create double colored molecular surface based on the electrostatic property to the receptor protein. The cavities or active sites were identified by the cavity prediction algorithm implemented in the software and potential binding sites of the receptor proteins identified appropriately. The numbers of cavities were set to five and parameters set to molecular surface with extended van der walls. The molecular docking was performed by utilizing MolDock simplex evolution search algorithm with grid resolution of 30 Å for grid generation and cavity predicted using MVD. The docking wizard runs with default parameters MolDock SE as a search algorithm, number of runs, maximum population and maximum iteration was restricted to 10, 50 and 1500 respectively. The selected modeled complexes were docked against the 3CL\textsuperscript{PRO} receptor protein and the best generated poses selected based on the MVD docking scores. The interaction between the ligands (complexes) and the receptor protein depends on the number of H-bonds, distance and binding energy. The ligand-protein interaction was fulfilled based on the ground state structures of the studied complexes obtained by GaussView software.

2.2.3. Validation of docking etiquette

The Ramachandran plot is possibly the best pointer for evaluating the quality of experimentally and theoretically premeditated determination of three dimensional protein coordinates [33, 34]. The docking protocol was validated using RAMPAGE which is an online server for verification of docking configuration based on RMSD of ligand-protein interaction or location of ligand atoms in the predicted and actual crystallographic determined binding mode. The confirmation was done by estimating the extent of ligand binding deviation from experimentally determined mode which is reported in form of the Ramachandran assessment plot and the superimposed structure and along with root-mean square deviation (RMSD).

3. Results and discussion

3.1. Geometrical analysis of rhenium complexes

The detail experimental synthetic methodologies along with the inhibitory activity assessment of the studied Re(I) tricarbonyl complexes against SARS-CoV-2 3CL\textsuperscript{PRO} main protease were reported by Karges et al. [13]. The eight (8) selected Re(I) tricarbonyl complexes herein denoted as A\textsubscript{1}, A\textsubscript{2}, A\textsubscript{3}, A\textsubscript{4}, A\textsubscript{5}, A\textsubscript{6}, A\textsubscript{7}, and A\textsubscript{8} have been identified to possess the strongest inhibitory effect which is the reason for the choice of the complexes for computational investigation and are reported in Fig. 2. All the studied complexes contain a 2,2-bipyridine ligand, single axial water (H\textsubscript{2}O) ligand, three (3) carbonyl ligands attached to the Re(I) central metal to form the six (6) coordinates Re(I) tricarbonyl complexes as presented in Fig. 2. Although all the studied complexes contain either of hydroxyl (-OH), carboxyl (-COOH), amino (-NH\textsubscript{2}), and methoxy (-OCH\textsubscript{3}) functional group substituents, they differ in the position of attachment within the bipyridine ligand. While complex A\textsubscript{1} has no functional group substituents (is unsubstituted), A\textsubscript{2} contains 2-methoxy (-OCH\textsubscript{3}) groups located at para-position on the bipyridine and is known as 4,4'-dimethoxy-2,2'-bipyridine metal complex. While complexes A\textsubscript{2} and A\textsubscript{6} have same hydroxyl (-OH) group at different positions, A\textsubscript{2} is para-functionalized known as 4,4'-dihydroxy-2,2'-bipyridine and A\textsubscript{6} is meta-functionalized known as 3,3'-dihydroxy-2,2'-bipyridine complexes. Similarly, complexes A\textsubscript{4} and A\textsubscript{5} have carboxylic acid as the substituents, however, A\textsubscript{4} is 4,4'-dicarboxy-2,2'-bipyridine (para-substituted) while A\textsubscript{5} is 3,3'-dicarboxy-2,2'-bipyridine (meta-substituted). In like manner, A\textsubscript{3} and A\textsubscript{8} are functionalized by amino (-NH\textsubscript{2}) groups and while A\textsubscript{8} is 3,3'-diamino-2,2'-bipyridine (meta-substituted) metal complexes.

3.1. Frontier molecular orbital (FMO)

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are very important parameters in quantum chemistry as they allow the investigation of chemical stability, reactivity, and provide the basis for calculating the quantum chemical descriptors using Eqs. (1)–(6) [22]. The HOMO energy signifies the donating ability while the LUMO energy is the accepting characteristics of the studied compound, thereby, necessitating electronic charge transfer from the HOMO to the LUMO. Furthermore, the energy difference between the HOMO and the LUMO is known as energy gap (\( E_g \)). Based on the FMO theory, the reactivity and stability of compounds would be determined by the difference in energy between the HOMO and LUMO of such compounds, hence, compounds with small and larger values of energy gap depicts a higher and lower reactivity and stability respectively [35]. This is true because electronic charge mobility between the HOMO and LUMO is paramount in a species with lower energy gap and vice versa for species with larger energy gap. The HOMO,

![Fig. 1. The Crystal Structure of 3CL\textsuperscript{PRO} (PDB: 6Y2F).](image-url)
Fig. 2. 3D structures of the studied complexes.
LUMO, energy gap, and global reactivity descriptors for the studied complexes calculated at B3LYP/6–31+G(d) level of theory is presented in Table 1 while the HOMO and LUMO orbitals isosurface and respective energy levels is presented in Fig. 3 and the fact-findings reveal a decreasing order in energy gap as thus: A8 > A3 > A1 > A5 ≥ A2 > A6 > A4 > A7. The carbonylic (-COOH) functionalized complexes, A4 and A7 have the relatively least energy gaps of 3.33 eV and 3.16 eV respectively while the hydroxyl (-OH) functionalized complexes, A8 revealed the relatively highest energy gap of 3.76 eV. This low-value in energy gap indicates that the carbonylic functionalized complexes are, based on frontier molecular orbital theory, the most reactive of the studied compounds while structure A4 is the most kinetically among the stable studied complexes. This DFT predicted observation is in perfect agreement with the in vitro observed experimental biological activities (IC50) which also reveal the carbonylic functionalized complexes to have the highest IC50 values relative to other complexes. The dicarbonyr acid (-COOH) substituents present in complexes A4 and A7 is an electron withdrawing group substituent attract electrons from the bipyrindine ligands toward itself and hence it will reduce the gap between HOMO-LUMO thus enhancing the transition of electrons. This ease in electronic mobility is responsible for the reactivity of the carbonylic functionalized complexes.

The molecular orbital composition which investigates the location, concentration, and distribution of FMOs in the complexes was also studied and also presented in Table 1. The predicted results was obtained as thus complex A8 having it HOMO distributed on Re197 with composition 53.10% and LUMO on C4 with composition 15.13%, the complex A4 has its HOMO situated on Re197 with composition 55.01% and LUMO on N38 with 12.01% as it composition, the HOMO distribution of A7 was found on Re17 with 64.39% and LUMO on C7 with 11.70%, for the A8 complex, the HOMO was on N38 and LUMO on N16 with 17.67% and 12.12% respectively, the HOMO and LUMO distribution on A1 was found on Re17 and C1 with 64.00% and 11.54%. Accordingly, while the HOMO for the complex A2 was found on 61.46% of Re19 and it LUMO on 14.57% of C7 the HOMO – LUMO distribution of A3 was on Re19 and C1 with 59.59% and 14.38% composition meanwhile, the HOMO and LUMO on A4 was observed to be Re19 and N17 with 63.47% and 11.23% as the orbital composition respectively. Generally, it was observed that the HOMO was predominantly delocalized on Re19 while the LUMO predominantly distributed on Carbon and Nitrogen atoms within the complexes.

3.2. Natural bond orbital (NBO) analysis

Natural bond orbital analysis is a significant tool for studying the interactions of donor and acceptor orbitals of molecules that enables the understanding of intra and intermolecular bonding and interactions. It is also a significant tool that is used for interpreting computational solutions of the Schrodinger equation into a more understandable and user-friendly chemical bond model [36]. The intensity of the donor – acceptor interactions is denoted by the second order perturbation energy E2. The stabilization energy E2 associated with the electron delocalization between the complexes under study is estimated using Eq. (7)

| Complex | HOMO/ eV | LUMO/ eV | E2/ eV | ω | S | μ | η |
|---------|----------|----------|--------|---|---|---|---|
| A1      | -9.96    | -6.33    | 3.63   | 18.26 | 0.28 | 8.14 | 1.82 |
| A2      | -9.69    | -6.08    | 3.61   | 17.24 | 0.27 | 7.89 | 1.80 |
| A3      | -9.46    | -5.79    | 3.68   | 15.86 | 0.27 | 7.62 | 1.84 |
| A4      | -10.13   | -6.79    | 3.34   | 21.46 | 0.30 | 8.46 | 1.67 |
| A5      | -9.18    | -5.56    | 3.62   | 15.01 | 0.28 | 7.57 | 1.70 |
| A6      | -9.82    | -6.03    | 3.78   | 16.61 | 0.26 | 7.93 | 1.49 |
| A7      | -10.04   | -6.88    | 3.16   | 22.68 | 0.31 | 8.46 | 1.58 |
| A8      | -8.98    | -5.54    | 3.44   | 15.34 | 0.30 | 7.26 | 1.72 |

3.3. Quantum theory of atoms-in-molecules (QTAIM)

The quantum theory of atoms-in-molecules (QTAIM) developed by Richard F.W, Baders and colleagues seek to define bonding using a topological analysis of density electron distribution [37]. This is because the concept of chemical bonding is not easily reconciled with quantum mechanical models of molecular system and as such, in order to understand deeply into the analysis of interaction between the metal and the bipyrindine ligands, the bond characteristics at BCP were investigated using Multifxw analyzer software version 3.7 dev [19].

The studied parameters under quantum theory of atoms-in-molecules investigated include density of electron at BCP, ρ(r), Laplacian of electron of density ∇2ρ(r), electron potential V(r), kinetic energy G(r), and total energy H(r) with much interest on the bond strength and are presented in Table 3 while other interactions are presented in Table S2 of the ESI. Since ρ(r) is related to the bond strength, the ρ(r) of N30–Re17 bond is 0.838 a.u. in A1 and it is much larger than 0.149 a.u. in A2 which indicate that C25–Re19 bond strength become weak, the bond between N17–Re19 was observed to have the electron density of 0.842 a.u. in A4 and C25–Re19 with strength of 0.151 a.u. in A4 the electron density of A3 was observed from the bond C25–Re17 with 0.150 a.u. A6, was from the bond C25–Re17 with 0.149 in A8 and 0.139 a.u. from this bond C22–Re19 in A7.

Generally, the bond strength ρ(r) of N30–Re17 with 0.838 a.u. was
Fig. 3. Optimized structure, HOMO, energy gap/eV, and LUMO of the studied complexes.
The Quantum theory of atoms-in-molecules (QTAIM) properties of the selected complexes.

Table 3

| Complexes | Donor (i) | Acceptor(j) | $E^\text{2J}/\text{kcal/mol}$ | $\Delta \rho_{ij}$ (i) | $\Delta \rho_{ij}$ (j) |
|-----------|-----------|-------------|-------------------------------|------------------------|------------------------|
| A1        | nC6       | n*C9        | 2123.35                       | 0.100                  | 0.139                  |
| A4        | nC6       | n*C9        | 1721.69                       | 0.101                  | 0.144                  |
| A3        | nC6       | n*C9        | 450.98                        | 0.040                  | 0.127                  |
| A2        | nC9       | n*C6        | 149.01                        | 0.090                  | 0.112                  |
| A5        | nReC7     | nReC26      | 119.49                        | 0.370                  | 0.212                  |
| A7        | nReC7     | nReC26      | 115.07                        | 0.380                  | 0.201                  |
| A6        | nReC7     | nReC26      | 109.93                        | 0.390                  | 0.208                  |

observed to be the strongest bond while the rest complexes show a weak bond indicating low inhibition ability. Moreover, the Laplacian of electron densities $\Delta^2 \rho(r)$ of the N30–Re19 increased from 0.359 to 0.576 also indicating the rupture trend of N30–Re19. The QTAIM was in general carried out to investigate the H-bond strength and the effect of the strong bond on the inhibition of some selected complexes.

3.4. Molecular electrostatic potential (MESP)

The molecular electrostatic potential mapping is a valuable tool in the field of computational chemistry that explained electron density throughout molecules. The electron density on various sections of the molecule indicates the compound’s electrophilic and nucleophilic sites, which provides a full description of the compound’s intermolecular interaction with the targets [38]. To provide much information on the site for the electrophilic and nucleophilic attacked, the electrostatic potential has been carried out on the studied complexes using the mapped file generated from the geometry optimization and the static potential has been carried out on the studied complexes using the Functional Information Theory (DFT). This MFCC method enables us to compute fully quantum mechanical ab-initio complex interaction energy and its gradient that are used in energy minimization, using Eq. (8). The interaction energy of these complexes under study can be deduced to follow the trend as thus: $A_3 < A_4 < A_5 < A_2 < A_7 < A_6 < A_1$ with the interaction energy associated as $-18.54,$ $-12.98,$ $-12.25,$ $-11.64,$ $-10.91,$ $-10.75,$ $-10.25,$ and $-3.57$ eV respectively as presented in Table S3 of the ESI. The negative energy values depicted by the complexes indicate stability and demonstrating the reaction to be exothermic. Substituted ligand complexes reveal higher interacting energies relative to the unsubstituted complex with a significant relative energy difference. Overview, the interaction energy study reveals how the functionalization of the bipyridine ligand with the substituents: $\text{-NH}_2$, $\text{COOH}$, $\text{-OH}$, and $\text{-OCH}_3$ increases the biological activities and reactivity of the metal complexes.

3.6. Aromaticity and charge distribution analysis

The aromaticity index is a property of conjugated cycloalkenes in which the stabilization of the molecule is enhanced due to the ability of the electrons in the $\pi$ orbital to delocalize. This objective is very crucial in the investigation of the biological activity of Re(I) tricarbonyl complex against SARS–CoV-2 as aromatic compounds are very vital in the biochemistry of all living things [40]. The observed HOMA aromaticity index evaluated according to Eq. (9) and the charge fragment is presented in Table S3 of the ESI. While the results of the aromaticity indices reveal a strong average value of 0.888 for all the studied compounds, the complexes $A_1, A_2, A_4, A_5,$ and $A_7$ possessed aromaticity values of 0.9095, 0.9064, 0.9115, 0.9010, and 0.9061. The results of the charge fragment obtained shows high correlation between the QTAIM; as the fragment in $A_1$ is correlated to electron densities and its Laplacian of electrons. The trend in charge fragment showed that $A_1$ possess the highest charge fragment which is accounted from the structural arrangement of the complexes. Furthermore, the individual atomic charge distributions of the selected complexes evaluated using the Mulliken population analyses are reported in Fig. 5.

3.7. Molecular thermodynamics

The thermodynamic molecular properties of the complex formation reactions were theoretically calculated to determine the free energy ($\Delta G$) and enthalpy change ($\Delta H$) of the studied complexes. The various molecular thermodynamic parameters of the studied complexes obtained using Eqs. (11) and (12) are presented in Table 4. The fact-finding show that complexes $A_7$ and $A_8$ possessed relatively highest and least enthalpy of formation having magnitude of $-609.27$ kcal/mol and $-21.66$ kcal/mol respectively. Conversely, complexes $A_3$ and $A_1$ presented higher negative values of $\Delta H$ and $\Delta G$ values which is correlated to electron densities and its Laplacian of electrons.
Fig. 4. Pictorial view of the Molecular electrostatic potential plots.
Fig. 5. Charge distribution based on Mulliken population analysis.
Table 4

Molecular thermodynamic parameters: correction to electronic energy (EE), zero-point vibrational energy (ZPE), total electronic energy (E_{tot}), enthalpy correction (H_{corr}), Gibbs free energy correction (G_{corr}), enthalpy change (ΔH), and Gibbs free energy change (ΔG).

| Ligand | CO | H_{2}O | Re^* | Complex |
|--------|----|--------|------|---------|
| EE_{corr}/a.u. | 0.166 | −113.310 | 0.024 | 0.001 | 0.231 |
| EE_{corr}/a.u. | 0.158 | −113.310 | 0.021 | 0.000 | 0.213 |
| E_{corr}/a.u. | −495.400 | −113.320 | −76.420 | −78.310 | −990.72 |
| H_{corr}/a.u. | 0.157 | 0.008 | −76.420 | −0.002 | 0.232 |
| G_{corr}/a.u. | 0.123 | −0.014 | −76.420 | −0.017 | 0.165 |
| E_{corr}+E_{ZPE}/a.u. | −495.240 | −113.310 | −76.420 | −78.910 | −990.510 |
| ΔG/(kcal/mol) | −78.910 | −78.310 | 0.23 | −0.191 | −0.55 |
| ΔH/(kcal/mol) | −78.910 | −78.310 | 0.191 | −0.191 | −0.55 |

Table 4 (continued)

| Ligand | CO | H_{2}O | Re^* | Complex |
|--------|----|--------|------|---------|
| EE_{corr}/a.u. | 0.166 | −113.310 | 0.024 | 0.001 | 0.231 |
| EE_{corr}/a.u. | 0.158 | −113.310 | 0.021 | 0.000 | 0.213 |
| E_{corr}/a.u. | −495.400 | −113.320 | −76.420 | −78.310 | −990.72 |
| H_{corr}/a.u. | 0.157 | 0.008 | −76.420 | −0.002 | 0.232 |
| G_{corr}/a.u. | 0.123 | −0.014 | −76.420 | −0.017 | 0.165 |
| E_{corr}+E_{ZPE}/a.u. | −495.240 | −113.310 | −76.420 | −78.910 | −990.510 |
| ΔG/(kcal/mol) | −78.910 | −78.310 | 0.23 | −0.191 | −0.55 |
| ΔH/(kcal/mol) | −78.910 | −78.310 | 0.191 | −0.191 | −0.55 |

show the relatively highest and lowest Gibbs free energy of −490.60 kcal/mol and −293.82 kcal/mol respectively. The general behavior in the enthalpy change of complex formation is follows: −609.27 > −572.00 > −473.24 > −329.00 > 223.65 > −85.09 > −37.03 > −21.66 kcal/mol associated with the formation of A_{7}, A_{8}, A_{9}, A_{10}, A_{11}, and A_{12} respectively. In like manner, the calculated Gibbs free energy change was observed to follow the pattern: −490.60 > 377.08 > −377.02 > −361.59 > −360.76 > −322.97 > −321.30 > −293.82 respectively associated with complexes A_{3}, A_{4}, A_{5}, A_{6}, A_{7}, A_{8}, and A_{9}, and A_{11}. The results of the enthalpy change for complexes A_{7} and A_{8} reveal that they are relatively more exothermic and this provides further justification for the highest biological effect of these complexes.

3.8. Density of states (DOS) analysis

The density of states (DOS) and partial density of states (PDOS) studies of the selected complexes was conducted to elucidate and gain deeper insight about the electronic structure along with the distribution of molecular orbitals with their associated energies with a complex [41, 42]. The DOS and PDOS plots of the studied complexes are presented in Fig. 6. The results reveal the complexes to have major molecular orbital composition constituting -p, -s, and -d orbitals. while the -p and -s orbitals have molecular orbitals contributions ranging from energies of −0.40 a.u. to 0.70 a.u. with the -p orbital having the maximum contributions at an energy of −0.55 a.u. −p orbital stretches and overlap with the -d orbital at an energy of −0.30 a.u. The results show the -d orbital contributions to be within the HOMO (broken lines) energy and ranging from −0.30 a.u. to −0.40 a.u. the electronic difference in the isomers can also be elucidated from the DOS and PDOS plot in Fig. 6. Most of the isomers can be distinguish by the degree of overlap of -p and -d orbitals around the HOMO level. It can be deduced from the hydroxyl group (-OH) complexes (A_{2} and A_{3}) isomers that while the A_{6} isomer has perfect overlap of -p and -d orbitals within the HOMO energy, the A_{2} isomer is observed to have a reduction in the -p orbital height relative to the -d orbital. The amino-functionalized isomers (A_{2} and A_{8}) reveal a -p and -d orbital DOS peak at the edge of the HOMO energy level with isomer A_{8} having the -p and -d orbital match at −0.358 a.u. Other isomers reveal -p and -d peak at the edge of the HOMO energy level, however, having different distributions of the orbital heights.

3.9. Molecular docking

Molecular docking simulations were performed to study the binding interactions between the selected ligands and the target SARS-CoV-2 viral protein, 3CLPRO. The receptor crystal structure of 3CLPRO was extracted from Protein Data Bank (PDB ID: 6Y2F) as provided by Zhang et al. [43]. The corresponding binding conformations of the docking protocol were selected based on their binding energies and hydrogen

E.A. Eno et al.

Chemical Physics Impact 5 (2022) 100105

10
bond interactions reported in Table 5. The docking results were validated using Ramachandran plot for each studied ligand as presented in Fig. S1(a)–(j) of the ESL.

The crystal structure, 3CLPRO was re-docked with its native ligand to ascertain and compare binding conformations with the candidate ligands. The RMSD value of the docked pose with its native ligand corresponds with the value, 2.557. The docking result of A1 with the crystal structure showed hydrogen bond interactions with SER158, ILE152 at a root mean square deviation value of 0.199. ASN151, ASP295, ILE152, ILE106 and SER 158 hydrogen bond interaction were highlighted for A2.

The receptor-A3 formed H-bond interactions with ASP153, CYS156, ILE152, ARG105, GLN110, THR111, ASP295 and THR292 as well as significant hydrophobic interaction with PHE294, VAL104, ILE106, and VAL104. For A4, with a RMSD value of 0.321, the hydrogen bond interactions were formed with GLN110, SER158, THR 111, ARG105, ILE152 amino residues and two hydrophobic interactions with PHE294.

Fig. 6. DOS and PDOS of the studied complexes.
and VAL104. In A5, more hydrogen bond interactions were discovered with residues ASN151, THR111, THR292, ASP295, ILE106, and at RSMD value of 0.837. The hydrogen bond interactions for A6 were with residues, GLN110, THR111 with no other significant interactions and at RSMD value of 0.852. In contrast, A7 showed more H-bond interactions with LYS102, ASN151, THR111, CYS105, GLN110 and few hydrophobic interactions with ASP153, PHE294 and at a higher RSMD value of 1.157. Furthermore, A8 interaction with the target protein shows comparatively lesser H-bond interactions and hydrophobic interactions with residues CYS156 and PHE294 respectively. The values of the RSMD of the 3CL\textsuperscript{PRO} and its native ligands shows higher deviation than those obtained with our candidate ligands, hence proving better ligand-protein conformation. The highlights of the 3D-binding modes of selected complexes (ligands) in the substrate-binding site of 3CL\textsuperscript{PRO} are displayed in Fig. 7 (a)–(j).

### Table 5

| Ligand ID | RSMD Values | Hydrogen Bond Residues | Other Interactions | Binding Energy (kJ/mol) | Re-rank Score |
|-----------|-------------|------------------------|-------------------|------------------------|---------------|
| A1        | 0.199       | SER158, ILE152         | VAL 104           | 70.536                 | 5.9211        |
| A2        | 0.154       | ASN151, ASP295, ILE152 | PHE294            | -91.5219               | -47.5084      |
| A3        | 0.770       | ASP153, CYS156, ILE152 | PHE294, VAL104, ILE106 | 83.8658               | -15.0497      |
| A4        | 0.321       | GLN110, SER158, THR111 | PHE294, VAL104.   | -97.2304               | -50.0103      |
| A5        | 0.837       | ASN151, THR111, THR292, ASP295, ILE106, GLN110 | PHE294 | -90.0875 | -44.8103 |
| A6        | 0.852       | GLN110, SER158, THR111 | PHE294, VAL104.   | -90.0875               | -44.8103      |
| A7        | 1.157       | LYS102, ASN151, THR111, CYS156, GLN110 | PHE294 | -107.254 | -57.4365 |
| A8        |             |                        |                   |                       |               |

3.10. Multilinear regression analysis (MLRA)

3.10.1. Model prediction

The best quantitative structure-activity relationship was established to demonstrate the correlations between physicochemical parameters (descriptors) and the biological activities (IC\textsubscript{50} numerical values) of structures. The compounds were investigated by MLRA using four descriptors, all of electronic descriptors including HOMO, LUMO, energy gap (E\textsubscript{g}), and interaction energy (E\textsubscript{int}). The obtained results show a very good correlation with an R\textsuperscript{2} value of 0.9942 as in Table 6 while the various electronic descriptors and the experimental IC\textsubscript{50} values are presented in Table S4 of the ESI. To check dependency between descriptors, different combinations of descriptors were performed from using a single descriptor to two, three and then four descriptors respectively. Using combinatorial approach of selection, all possible combinations were made. Before carrying out MLRA, correlation

![Fig 7.](image-url)
coefficient value was calculated for each pair of descriptors and hence, dependencies between descriptors were seen. In order to select the best QSAR model, several QSAR equations were modeled and tested on the basis of the following statistical parameters: the correlation coefficient, R, measures the degree of linear association between two variables; the standard error of the estimate, an absolute measure on the quality of fit; the squared correlation coefficient which represent the relative measure of the quality of fit and finally the F value known as the Fischer variance due to error in the regression. The resulted high F values obtained from the model show that the model is statistically significant. The best model, which is the most statistically significant correlation generated from the model show that the model is statistically significant. The best model, which is the most statistically significant correlation generated after MLRA using the BuildQSAR software \cite{44,45} is given in Eq. (13) along with the relevant statistical parameters.

\[
\text{IC}_{50} = -195.23H + 183.57L - 205.01E_{g} - 1.25E_{int} - 37.18
\]  
(13)

\[R = 0.997; R^2 = 0.994; \text{adjusted } R^2 = 0.971; Q = SE = 0.986; F = 42.688; n = 6\]

Where R is the coefficient of correlation, F is the Fischer statistic, n is the number of compounds, SE is the standard error of estimation. The calculated F values of the QSAR model obtained are more than the F value tabulated by a large margin. This indicates the significant of the regression. For the present model, the F value was seen to be statistically significant at 95% level. The accuracy of this model is obtained from the low standard deviation. We consider a model for validation when the \(R^2 > 0.6\). The present model indicates a strong correlation between the independent variables and dependent variable with R and \(R^2\) values of 0.997 and 0.994 respectively.

### 3.10.2. Model validation

To measure the accuracy of prediction, it is necessary to find out how predictive the model would operate, “Leave-one-out” (LOO) cross-validation method was used to validate the predictive power of the model in Eq. (13). Cross-validation is used as a result of its reliability and convenience to test the significance of a model \cite{46}. Hence, the resulted MLR model was validated by checking the validity of its predictive power and the following statistical parameters were used to validate the developed model: Adjusted R, \(P_{\text{PRESS}}\) (sum of the predicted residual squares), PE (predictive error of the model), SSY (sum of squares of response value), \(S_{\text{PRESS}}\) (prediction uncertainty) and \(R_{2\text{CV}}\) (global predictive ability). The values of these parameters are given in Table 7. A good approximation of actual predictive error of the model is obtained by the use of \(P_{\text{PRESS}}\). The predictions of the model are better than chance if the \(P_{\text{PRESS}}\) value is lower than SSY value. The obtained \(P_{\text{PRESS}}\) value of 0.97115 indicates that the model is statistically significant. Checking further the reliability of the model, the \(P_{\text{PRESS}}/\text{SSY}\) ratio should be less than 0.4 \cite{47}. As shown in Table 5, the ratio of the developed model is 0.00582. An indication of the performance of the model can be obtained from its \(R_{\text{adj}}^2\) value. High \(R_{\text{adj}}^2\) values are essential in order to ensure good performance of the QSAR model, and hence, \(R_{\text{adj}}^2 = 0.971\) were obtained for the QSAR model respectively. The predictive power of the model is further investigated using the PE (predictive error of the correlation coefficient). The present model satisfies the condition \(R > 6\text{PE}\), therefore the model in Eq. (13) has a good predictive power. The predictive uncertainty (\(S_{\text{PRESS}}\)) is another important parameter. The lower \(S_{\text{PRESS}}\) value of 107.554 indicates the predictive ability of the model is good. The plot of linear regression between the predicted and experimental values of the biological activities is presented in Fig. 8(a) with good correlation of \(R^2 = 0.994\). The test set has a good distribution along the range of values of the training set. Hence, the QSAR model developed in the current study can be successfully applied to predict the biological activities (\(\text{IC}_{50}\)). The presence of systemic error in the QSAR model is being investigated by the plot in Fig. 8(b). Residuals of the predicted values of the \(\text{IC}_{50}\) were plotted against the experimental values. No systemic error since the propagation of the residuals is on both sides of zero.

### 4. Conclusion

Detail DFT studies, in silico molecular docking, and multilinear regression analysis (MLRA) investigations of eight (8) selected biologically active Rhenium Tricarbonyl complexes design and modeled based on the results of Karges and co-workers is presented in this study. Atomicist DFT modeling has been conducted to investigate the reactivity, structural stability, and electronic properties based on frontier molecular orbitals (FMO), natural bond orbitals (NBO), interaction energies, density of states (DOS), charge distributions, and molecular thermochemical parameters. Molecular docking simulations have also been performed to study the binding interactions between the selected biologically active complexes and the target SARS-CoV-2 viral protein, 3CL\text{PR}O\text{R}. Quantitative structure-activity relationship (QSAR) has been established to demonstrate the correlations between the DFT calculated descriptors and the in vitro biological activities (\(\text{IC}_{50}\)) of the structures. The result obtained from the energy gap indicate that the carboxylic functionalized complexes are the most reactive complexes while complex A4 is shown to be the most kinetically stable complex. Complex A3 has the highest interaction energy which has been correlated with the type of functional group present on the molecule and thus it is perceived to possess the highest inhibitory activity against the studied protein complex. Thermodynamic considerations of the studied systems supposed the complexes to be exothermic and spontaneous. In summary, all the quantum chemical calculation investigated in this study shows excellent agreement with the experimentally determined data and thus point the Re (1) tricarbonyl complexes as promising candidates for the development of effective SARS-CoV-2 inhibitors.

### Table 6

Selected values of correlation coefficient (\(R^2\)) for the studied complexes by the combination of 4, 3, 2, and 1 electronic descriptors.

| Descriptors | \(R^2\) 1 | \(R^2\) 2 | \(R^2\) 3 | \(R^2\) 4 |
|-------------|----------|----------|----------|----------|
| HOMO, LUMO, \(E_{g}\), \(E_{int}\) | 0.997 | HOMO, LUMO, \(E_{g}\) | 0.853 | HOMO, LUMO | 0.799 | HOMO | 0.624 |
| HOMO, LUMO, \(E_{g}\) | 0.976 | HOMO, \(E_{g}\) | 0.792 | LUMO | 0.782 |
| \(E_{g}\), \(E_{int}\), HOMO | 0.979 | HOMO, \(E_{g}\) | 0.723 | \(E_{int}\) | 0.184 |
| \(E_{g}\), \(E_{int}\), LUMO | 0.977 | LUMO, \(E_{g}\) | 0.797 | \(E_{g}\) | 0.003 |
| \(E_{int}\), LUMO | 0.946 | LUMO, \(E_{int}\) | 0.213 |

### Table 7

Cross-validation parameters.

| Model | \(P_{\text{PRESS}}\) | SSY | \(P_{\text{PRESS}}/\text{SSY}\) | \(S_{\text{PRESS}}\) | \(R^2\) CV | \(R^2\) adj | 6PE |
|-------|-----------------|-----|------------------|-----------------|-------------|-------------|-----|
| 1     | 0.97115         | 166.793 | 0.00582         | 107.554        | 0.994       | 0.971       | 107.554 |
Fig. 8. (a) Plot of linear regression between the predicted and experimental values of the biological activity, and (b) Plot of residuals of the predicted values of the IC50 were plotted against the experimental values.

Data and software availability

All data are contained within the manuscript and manuscript supporting information document (ESI).

CRediT authorship contribution statement

Ededet A. Eno: Formal analysis, Writing – review & editing. Hitler Louis: Project administration, Visualization, Supervision. Tomsmith O. Unimuke: Formal analysis, Writing – review & editing. Terkmumbur E. Gber: Formal analysis, Writing – review & editing. Josephat A. Akpanke: Formal analysis, Writing – review & editing. Ismail O. Amodu: Resources, Validation. Amanda-Lee E. Manicam: Visualization. Offiong E. Offiong: Formal analysis, Writing – review & editing.

Declaration of Competing Interest

All authors declare zero conflict of interest.

Acknowledgments

This work did not receive any financial support from any organization. However, the authors are thankful to the centre for high performance computing (CHPC), South Africa for the computational resources.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.chphi.2022.100105.

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