



How to face COVID-19: proposed treatments based on remdesivir and hydroxychloroquine in the presence of zinc sulfate. Docking/DFT/POM structural analysis

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ABSTRACT

Remdesivir and hydroxychloroquine derivatives form two important classes of heterocyclic compounds. They are known for their anti-malarial biological activity. This research aims to analyze the physico-chemical properties of remdesivir and hydroxychloroquine compounds by the computational approach. DFT, docking, and POM analyses also identify antiviral pharmacophore sites of both compounds. The antiviral activity of hydroxychloroquine compound's in the presence of zinc sulfate and azithromycin is evaluated through its capacity to coordinate transition metals (M = Cu, Ni, Zn, Co, Ru, Pt). The obtained bioinformatic results showed the potent antiviral/antibacterial activity of the prepared mixture (Hydroxychloroquine/Azithromycin/Zinc sulfate) for all the opportunistic Gram-positive, Gram-negative in the presence of coronavirus compared with the complexes Polypyridine-Ruthenium-diaquo. The postulated zinc(II) complex of hydroxychloroquine derivatives are indeed an effective antibacterial and antiviral agent against coronavirus and should be extended to other pathogens.

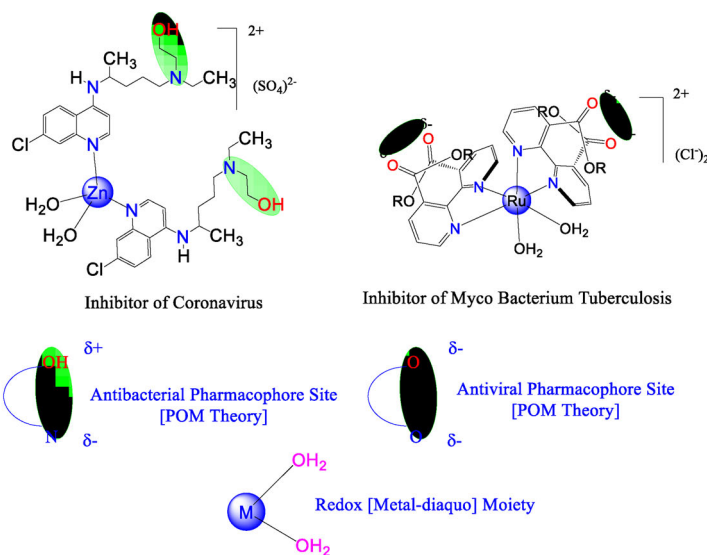
The combination of a pharmacophore site with a redox [Metal(OH)₂]₂ moiety is of crucial role to fight against viruses and bacteria strains.

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1. Introduction

Coronavirus is one of the most recent leading causes of mortality worldwide. The limited success of currently used antiviral drugs is a driving force for searching of new compounds with antiviral potential (Fang & Lerner, 2020). A limited number of such compounds are being tested against coronavirus in laboratories worldwide (Hoft, 2020; Hunt, 2020; Subramanian, 2020). The main challenge is to find a relatively simple, efficient, and generally synthetic method that enables the preparation of libraries of anti-corona drugs containing one or more pharmacophoric groups (hybrid molecules) with hope for new, effective anti-corona agents. In addition, great attention of world chemists is given to the new treatments of COVID-19, which have been proposed by French, Chinese, and American Governments.

On January 27th/2020, science published a news release suggesting that the ideal treatment for 2019-nCoV is likely combine a drug called Remdesivir and monoclonal antibodies. Remdesivir is thought to be effective for both MERS and new coronaviruses. In a mouse study led by Ralph Baric of the University of North Carolina, published in the journal Nature-Communications, the study tested interferon beta-1b with Remdesivir, an experimental drug manufactured by Gilead, USA.

On the other hand, the study published online Friday night, by the controversial Professor Didier Raoult and the Marseille University Hospital Institute (IHU), involving 80 peoples, was immediately criticized by the scientific community. Carried out without a control group, it still does not confirm the beneficial

effect of hydroxychloroquine on the symptoms and the evolution of COVID-19. The positive development and the drop in viral load observed could be natural or not. The first results of the most framed European clinical trial Discovery, which includes hydroxychloroquine, could be known by the weekend, said Monday, March 30, 2020, Frédérique Vidal, the Minister of French Research (Richard & Gambert, 2020).

Lack of time, and to avoid more stress resulting of innocent Americans death, Sir President Donald Trump and his Government-authorized without hesitation this synergetic combination to fight with highly pathogenic coronavirus for five days: 1-Hydroxychloroquine (200 mg), 2 Azithromycin (500 mg), 3-Zinc sulfate (220 mg) (Figure 1).

Molecular modeling has become a very practical and powerful tool. This approach is an application of theoretical calculation methods to explain the molecular structure problems and chemical reactivity (Liotta, 1988). In the domain of the study of the reactivity of organic and pharmaceutical molecules, the researchers have encountered two main problems. The first problem concerns the explanation of the reactivity of some compounds in comparison to others. In addition, the second difficulty is to explain why some sites of the molecule are more reactive than other sites. To solve these problems, several theories have been established for the study of the chemical reactivity. Such as the transition state theory (Eyring, 1931), Frontier Molecular Orbital Theory (Fukui et al., 1952), Hard and Soft Acids and Bases Theory (Pearson, 1963), and the density functional theory (DFT) (Klopman 1968).



Remdesivir (RMDS)

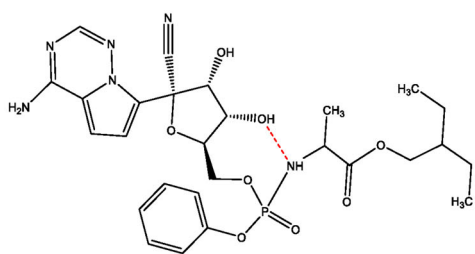


Hydroxychloroquin (HCQS)

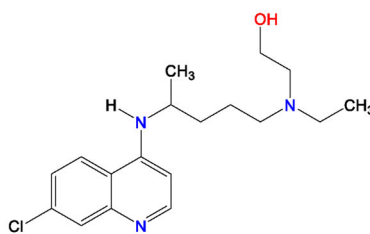


Azithromycin (AZTM)

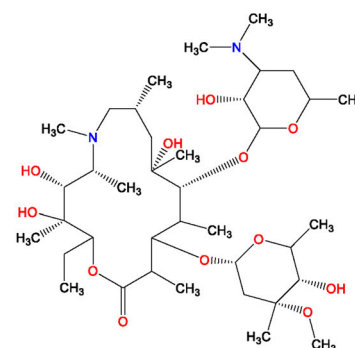
Figure 1. Proposed known antipaludism drugs to fight against COVID-19.



Remdesivir (RMDS)



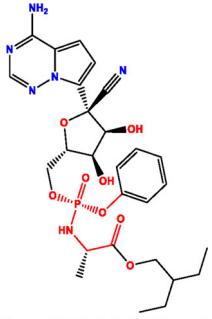
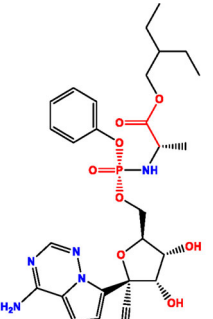
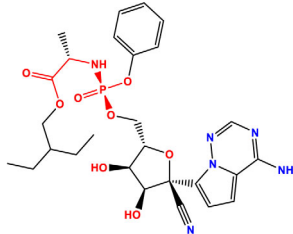
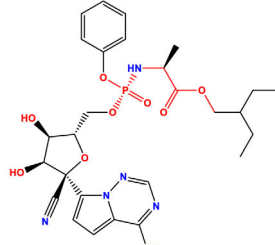
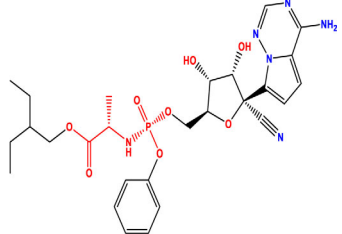
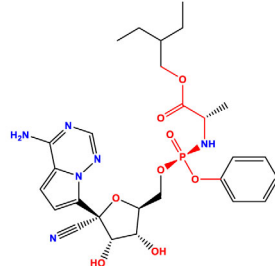
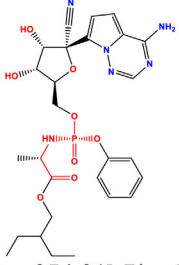
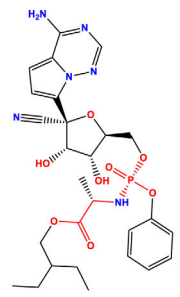
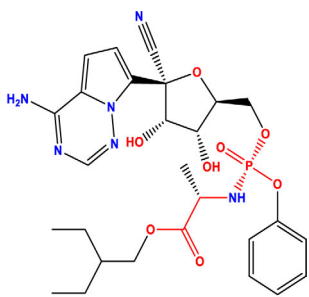
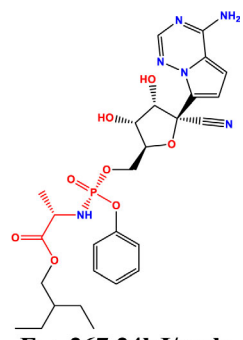
Hydroxychloroquin (HCQS)



Azithromycin (AZTM)

Figure 2. Molecular structure of proposed new anti-Covid-19 drugs.

Table 1. Energy (kcal/mole) of different conformers of Remdesivir.

Entry	Structure	Entry	Structure
C1	 E= -356.90 kJ/mole	C6	 E= -300.06kJ/mole
C2	 E= -355.54kJ/mole	C7	 E= -298.57kJ/mole
C3	 E= -354.59kJ/mole	C8	 E= -296.49kJ/mole
C4	 E= -354.31kJ/mole	C9	 E= -291.58kJ/mole
C5	 E= -353.71kJ/mole	C10	 E= -267.24kJ/mole

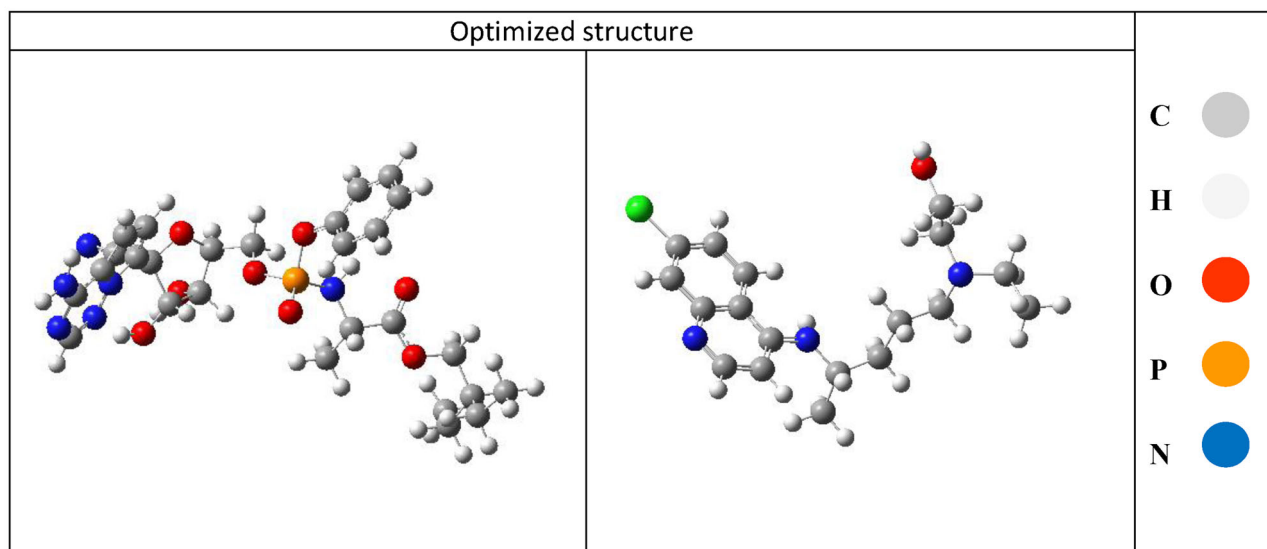


Figure 3. Optimized structure of Remdesivir and Hydroxychloroquine obtained at B3LYP/6-31G (d) level in Gas phase.

Table 2. Calculated E_{HOMO} , E_{LUMO} , ΔE_{gap} , and quantum molecular descriptors of Remdesivir and Hydroxychloroquine.

Molecular descriptors	Remdesivir	Hydroxychloroquine
Log P	3.2	2.87
α_{Tot} (Bohr ³)	353.11	231.68
Total Energy (a.u.)	-2321.63	-1401.2388
E_{LUMO} (eV)	-1.2438	-1.1632
E_{HOMO} (eV)	-6.0790	-5.6711
ΔE_{gap} (eV) $E_{\text{HOMO}} - E_{\text{LUMO}}$	4.8352	4.5079
Ionization Potential ($I = -E_{\text{HOMO}}$)	6.0790	5.6711
Electron Affinity ($A = -E_{\text{LUMO}}$)	1.2438	1.1632
Chemical hardness ($\eta = (I - A)/2$)	2.4176	2.2539
Chemical softness ($s = 1/2 \eta$)	0.2068	0.2218
Chemical Potential ($\mu = -(I + A)/2$)	-3.6614	3.4171
Electronegativity ($\chi = (I + A)/2$)	3.6614	-3.4171
Electrophilicity index ($\omega = \mu^2/2 \eta$)	2.7725	2.5903

In fact, the organic/organometallic synthesis constitutes an important field in the synthesis of novel bioactive molecules, particularly heterocyclic ones bearing anti-coronavirus bioactivity (Richard & Gambert, 2020). The hydroxychloroquine is an important nucleus, thanks to its structure (Figure 2), which contains various nucleophilic and electrophilic reactive sites, which may yield to the synthesis of transition metal complexes.

According to the World health organization, 42,512,186 confirmed cases with 1,147,301 deaths and 215 countries affected by coronavirus. By reports, most confirmed cases reported by the Americas (1,147,301) and the death cases (222,507), which is presently spreading by community transmission. The first wave of COVID-19 is still going on, but in some countries, the 1st wave was over, and the second wave was expected to increase. Although coronavirus is a global pandemic, no particular drugs or vaccines for this viral disease are still available. The treatment is suggestive, and oxygen therapy symbolizes the initial phase for the respiratory deficiency (Wang et al., 2020; Xu et al., 2020). At present, the immunization against coronavirus infection is not scientifically confirmed. In the research, various compounds from other viral infections have been repurposed to treat COVID-19, but the treatment advantage has, in many cases, been minimal or non-existent (Rakib et al., 2020).

We report the docking, DFT, and POM analyses of newly proposed treatments in the current training. The three products are subjected to comparative study. In addition, the influence of the substituents carried by the aromatic nucleus on the antibacterial and antiviral activities is emphasized. The observed anti-COVID-19 and antibacterial activities are interpreted through the analysis of DFT/Docking/POM calculations. The presence of Zinc sulfate in the American treatment presents a crucial role because its presence with hydroxychloroquine as N-ligand monodentate lead us to the formation of the complex with a potential antiviral activity, carrying two optional therapeutic functions

2. Materials and methods

2.1. DFT calculations

The optimization of the molecular structure was accomplished by integrating the functional three-parameter exchange of Becke (1993), with the functional Lee-Yang-Pear association (Lee et al., 1988). The method (B3LYP) with a basis set of 6-31G(d) is applied with the software package Gaussian 9.0. HOMO-LUMO energy differences have been

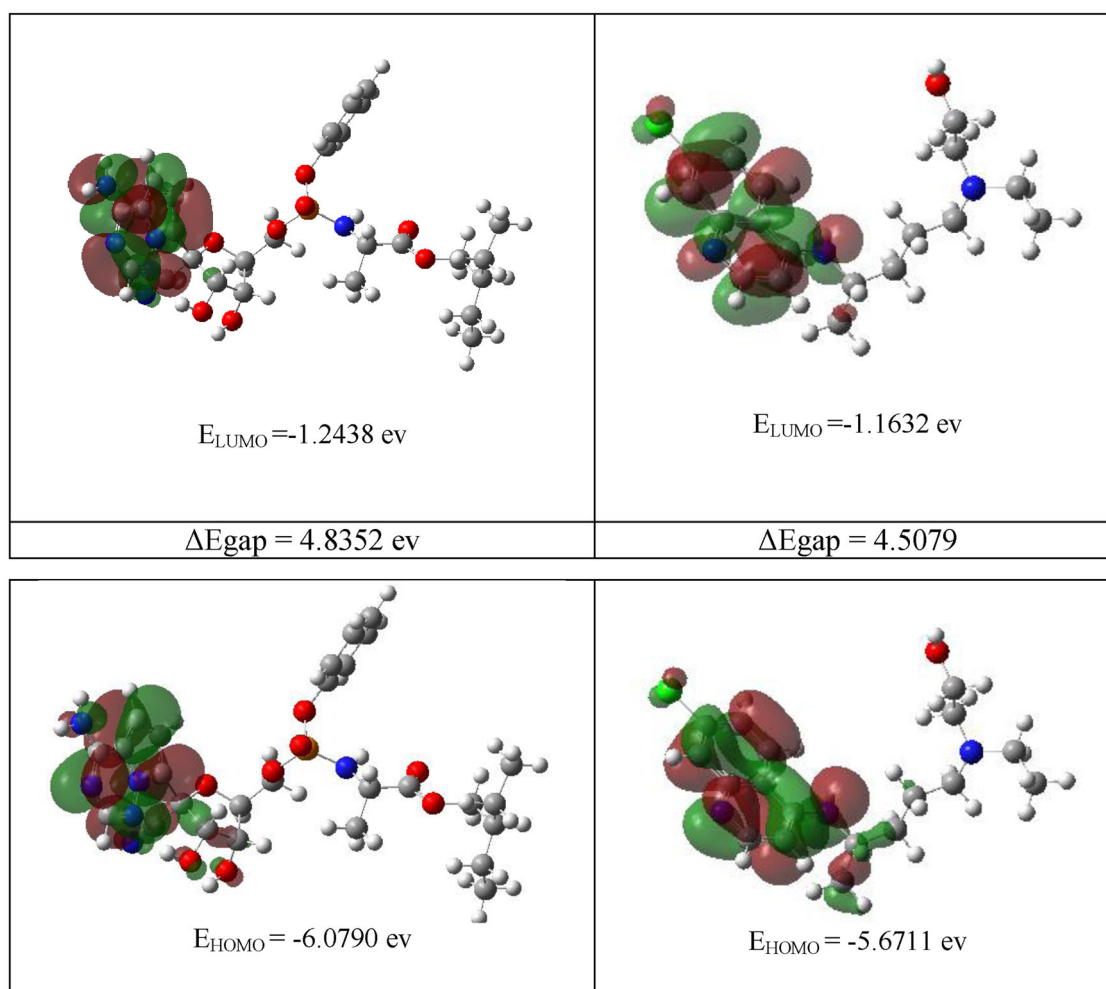


Figure 4. HOMO, LUMO orbitals and their energy gap (ΔE_{gap}) for Remdesivir and Hydroxychloroquine.

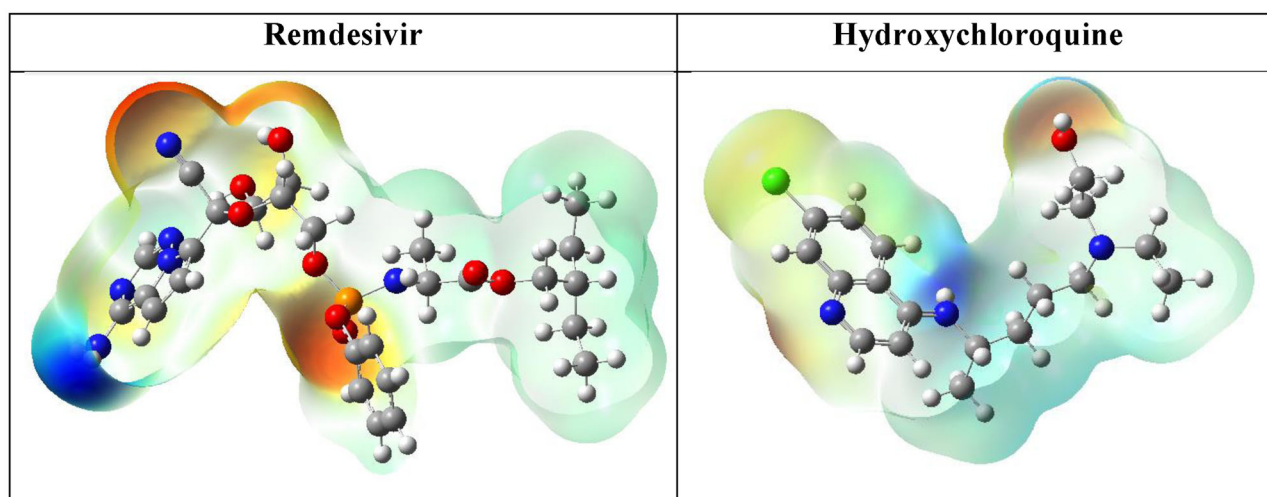


Figure 5. Molecular electrostatic potential MESP for Remdesivir and Hydroxychloroquine.

Table 3. Mulliken charge of Remdesivir.

N-P	-0.727	P-O-CH ₂	-0.520	Antiviral pharmacophore site
O = P	-0.562	C = O	-0.491	(P = O ^{δ-} δ-O = C)
P-O-cycle	-0.617	O = C-O	-0.466	

obtained to understand the stability and reactivity of compounds. Mulliken charges were calculated for molecular polarization and electronic structure.

2.2. Molecular docking

2.2.1. Selection of protein structure from protein data bank

The three-dimensional coordinates of COVID-19 M^{Pro} in complex with peptidomimetic inhibitor, N3, (PDB ID: 6LU7) were downloaded from the Protein Data Bank (PDB, <https://www.pdb.org/>).

rcsb.org/). Water molecules were removed from protein structure using BIOVIA Discovery Studio 4.5 (Dassault Systems, USA).

2.2.2. Generation of ligand data

The 3D structure of remdesivir was optimized using the molecular mechanics force field (MM+) (Hocquet & Langgard, 1998) and subsequently by the semiempirical PM3 method (Stewart, 1989) using the Avogadro 1.2.0 (University of Pittsburgh, Pittsburgh, PA, USA). Water molecules were removed using BIOVIA Discovery Studio 4.5 (Dassault Systems, USA).

2.2.3. Molecular docking using discovery studio

Genetic parameters for molecular docking were set on: population size 300; generations 100; the number of solution or poses: 10. Remdesivir was docked into the binding site, and after the docking procedure, protein-compound interaction profiles of electrostatic (Elec), hydrogen-bonding (H-bond), and van der Waals (vdW) interactions were generated. Docking poses were ranked by combining the pharmacological interactions and energy-based scoring function (E) is: $E = \text{vdW} + \text{H-bond} + \text{Elec}$. Results were viewed and analyzed with BIOVIA Discovery Studio (Ver 4.5).

Table 4. Energies of the main interactions COVID-19 Mpro residues and ligand Remdesivir (M = main chain; S = side chain).

H bond	Energy/kcal/mol	van der Waals interaction	Energy/kcal/mol
S-THR 24	-6.98	M-THR 24	5.17
S-THR 25	-3.5	S-THR 25	4.93
S-THR 45	-3.5	S-MET 49	5.97
S-SER 46	-6	M-LEU 141	5.43
M-GLY 143	-3.5	M-ASN 142	11.57
M-SER 144	-3.5	S-ASN 142	9.75
M-CYS 145	-3.5	M-GLY 143	8.43
S-CYS 145	4.28	M-SER 144	4.09
		M-CYS 145	4.27
		M-HIS 164	4.27
		M-LEU 4	7.55

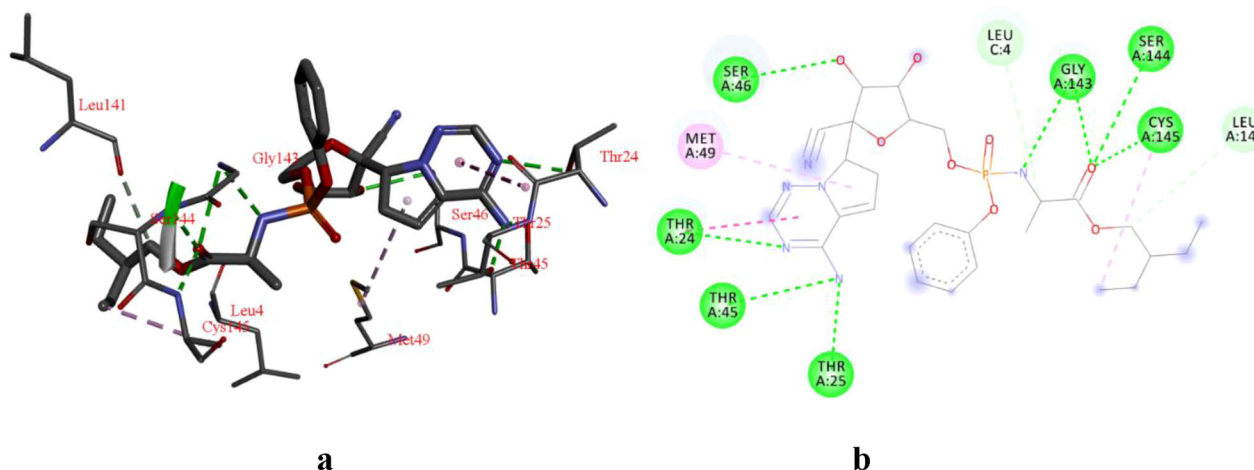


Figure 6. (a) 3D representation and atomic charge surface of the binding site. (b) Interactions of Remdesivir with residues binding site of COVID-19 Mpro.

2.3. Mechanism of docking

Docking was accomplished by iGEMDOCK molecular docking software (Hsu et al., 2011). During docking, at first, the molecules were prepared, and bonds, bond orders, explicit hydrogen's, charges, flexible torsions were assigned to both the protein and ligands. From the docking, wizard ligands were selected, and the scoring function used was iGEMDOCK score. If hydrogen bonding is likely, the hydrogen bond energy contribution to the docking score is assigned a penalty based on the deviations from the ideal bonding angle. This prospect can significantly reduce the number of unlikely hydrogen bonds and also internal electrostatic interaction; internal hydrogen bond sp^2-sp^2 torsions are calculated from the pose by enabling the ligand evaluation terms.

The search algorithm is taken as iGEMDOCK and numbers of runs taken are 10, and max interactions were 2000 with population size 300 and with an energy threshold of 100 also at each step least 'min' torsions/translations/rotations are tested and the one giving lowest energy is chosen. If the energy is positive (i.e. because of a clash or an unfavourable electrostatic interaction), then additional 'max' positions will be tested. If the pose being docked is closer to one of the

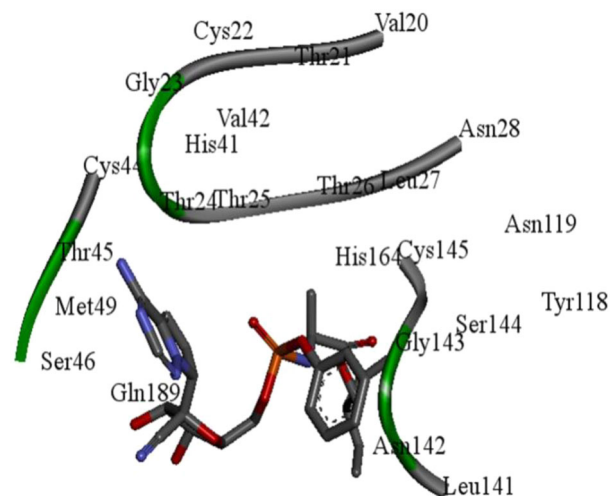


Figure 7. The binding site of COVID-19 Mpro with docked inhibitor Remdesivir.

ligands in the list than specified by the Root Mean Square Deviation (RMSD) threshold, an additional penalty term (the energy penalty) is added to the scoring function. This ensures greater diversity of the returned solutions since the docking engine will focus its search on poses different from earlier poses found. The energy penalty was set to 100, the RMSD threshold was 2.00, and RMSD calculation by atom ID (fast) was set. Docking was conducted between protein and drugs, which results in binding affinities in kcal/mol and docking run time. The compound which gives lowest binding energy is chosen as the best inhibitor. iGEMDOCK showed better overall performance in docking simulations when compared with other software.

2.4. Petra/Osiris/Molinspiration (POM) analyses

Assessments of Petra/Osiris/Molinspiration (POM) were used to determine the pharmacophore site type and to evaluate

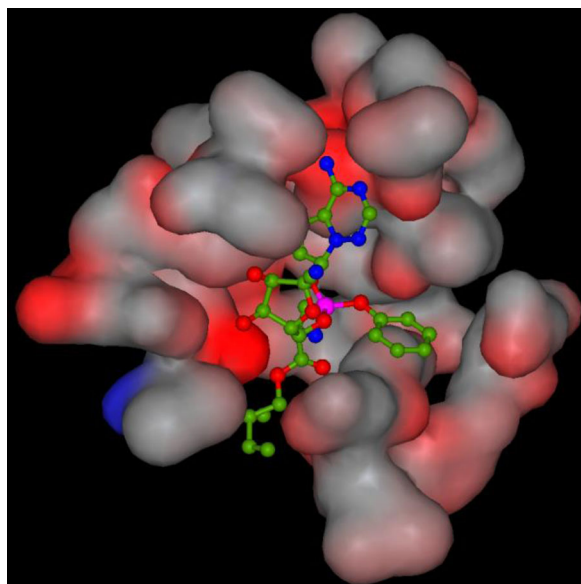


Figure 8. Potential surface representation of COVID-19 Mpro binding site with docked inhibitor Remdesivir. (Range of potential: from min. 1.77 mV (blue) to max. 0.541 mV (red)).

the impact of the position and physical/chemical properties of substituents affecting biological activity. The presence of several side effects is a major concern associated with synthetic drugs. In addition to an excellent biological action, a drug molecule must have an excellent pharmacokinetic profile in the biological system. In the in silico method, Petra/Osiris/Molinspiration (POM), authenticated by almost 7,000 drug molecules that are available on the market, we have used well-known pharmacokinetic profiles in comparison with the five rules of Lipinski that found bio-availability predictions imperfectly (Ben Hadda et al., 2020).

3. Results and discussion

3.1. DFT calculation of remdesivir

The geometrical, electronic, and energy parameters were extracted from GaussView 5.0 program based on the optimized structures (Francl et al., 1982; Frisch, 2009). The molecular geometry of remdesivir and their substituents' nature is

Table 5. Osiris calculations of toxicity risks of compounds.

Compd.	MW	Toxicity risks ^[a]				Osiris calculations ^[b]			
		MUT	TUM	IRRI	REP	cLogP	cLogS	DL	DS
RMDS	602	+++	---	---	---	0.31	-4.99	-30.36	0.05
HCQS	335	---	+++	+++	+++	3.08	-3.55	6.54	0.48
AZTM	748	+++	+++	+++	+++	1.66	-3.09	13.85	0.48

RMDS: Remdesivir, HCQS: Hydroxychloroquin, AZTM: Azithromycin. Highly toxic: (---), slightly toxic: (+), Not toxic (+++). ^[a] MUT: Mutagenic, TUM: Tumorigenic, IRRI: Irritant, RE: Reproductive effective. ^[b] cLogS: Solubility, DL: Druglikeness, DS: Drug-score.

Table 6. Molinspiration calculations of compounds.

Compd.	Mol inspiration calculations ^a					Drug-likeness ^b				
	TPSA	nOHNH	NV	VOL	GPCRL	ICM	KI	NRL	PI	EI
RMDS	204	5	2	523	0.27	-0.35	0.20	-0.48	0.49	0.38
HCQS	48	2	0	321	0.35	0.30	0.44	-0.12	0.12	0.15
AZTM	180	5	2	736	-0.60	-1.50	-1.40	-0.28	-0.82	

RMDS: Remdesivir, HCQS: Hydroxychloroquin, AZTM: Azithromycin.

^aTPSA: Total molecular polar surface area; nOHNH: number of OH and NH interaction, NV: number of violation of five Lipinsky rules; VOL: volume.

^bGPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor.

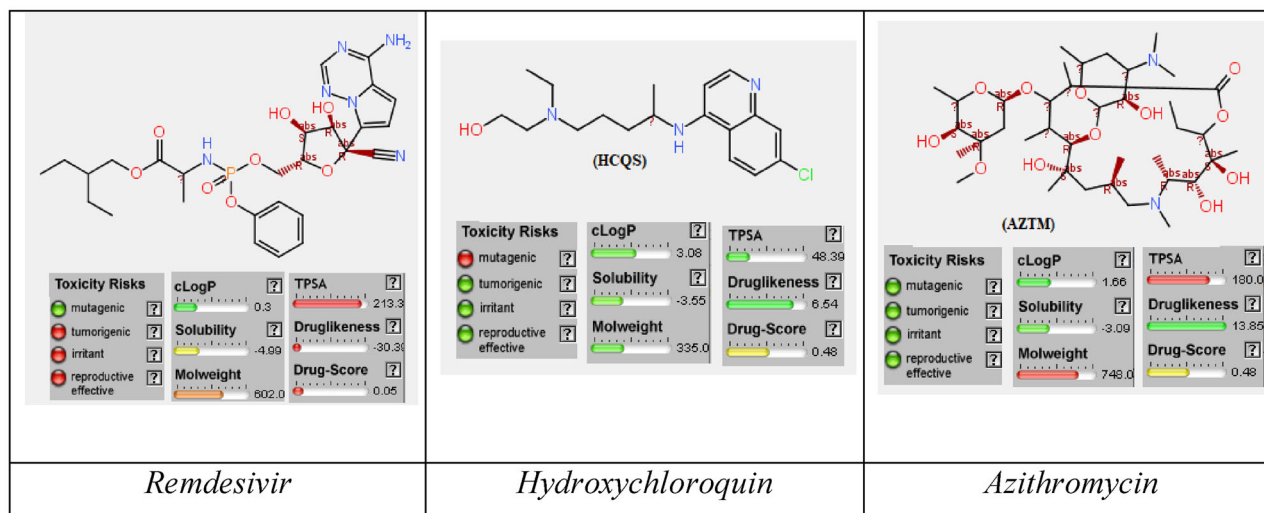


Figure 9. Osiris calculations of Remdesivir, Hydroxychloroquin and Azithromycin, respectively.

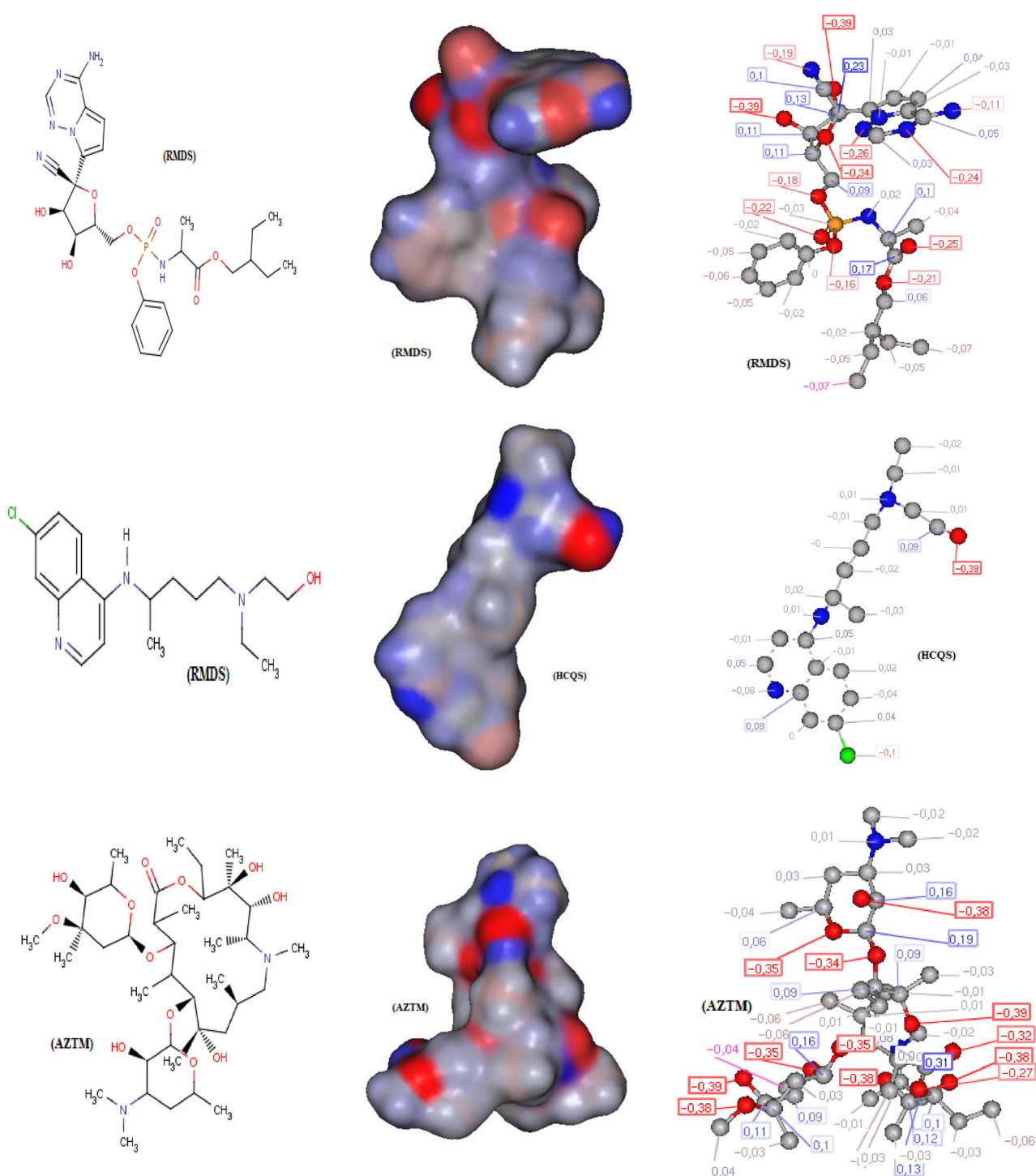


Figure 10. Atomic charges of anti-COVID-19 agents.

often correlated with their stability and reactivity. To specify the relationship between the experimental results of the activities with the structure of the molecules and to evaluate this relationship, theoretical studies were carried out by molecular modeling. Thus, modeling gives some important and necessary information on the structure and reactivity of remdesivir.

3.2. Conformational determination

The conformation of a molecule influences its physical and chemical properties. Therefore, reliable conformational

analysis plays a key role in the understanding of structure. Initial conformational searching of the title compound C1 was performed by the Spartan 8.0 program (Deppmeier et al., 2002) with MMFF (Brintzinger et al., 1999; Huang et al., 2006) molecular mechanics force field (Table 1).

In this study, molecular modeling was used to study the studied compounds' reactivity to determine the most stable structure (Figures 3). The results show that the molecular structure of DFT optimization is consistent with the crystal structure determined by X-ray single crystal diffraction (Siegel et al., 2017).

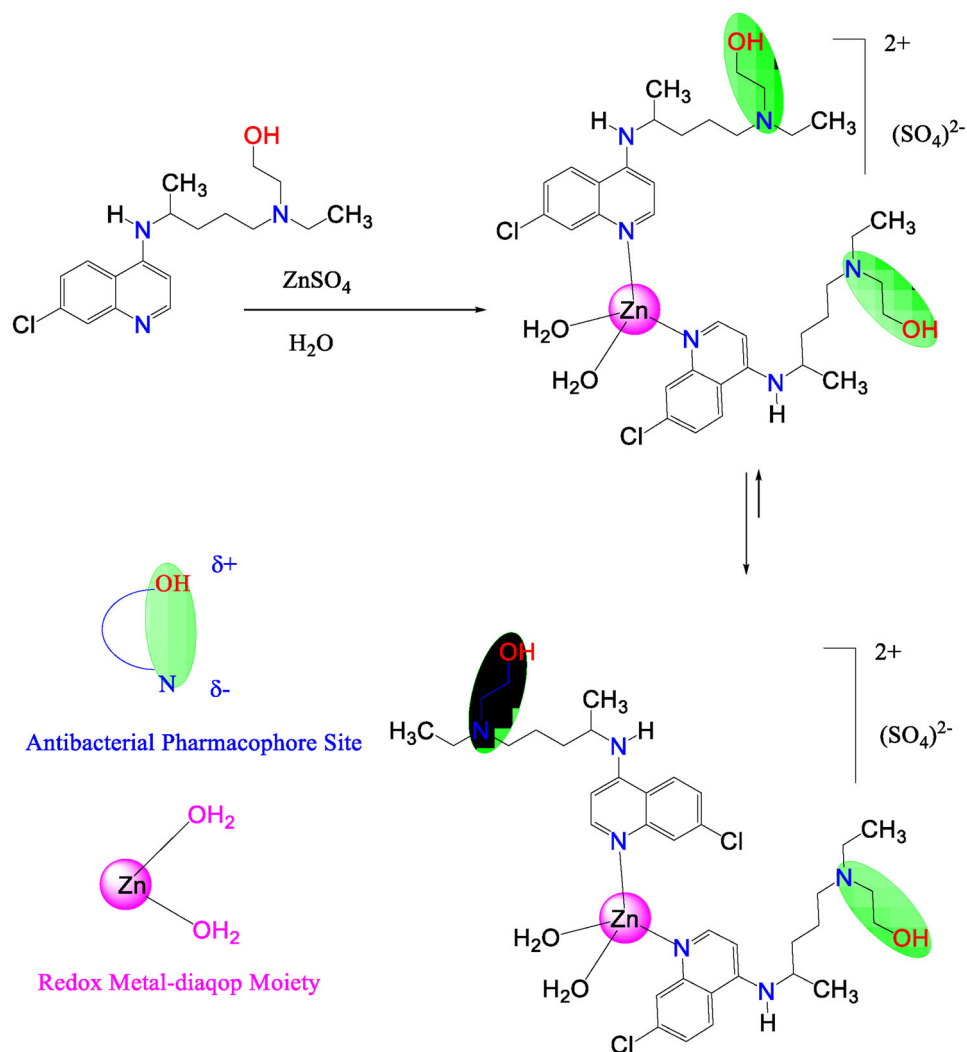


Figure 11. Hypothetic molecular structure of resulting Zinc complex of Hydroxychloroquine bearing antibacterial N,O,H-pharmacophore site antiviral redox $[Zn(OH_2)_2]$ moiety.

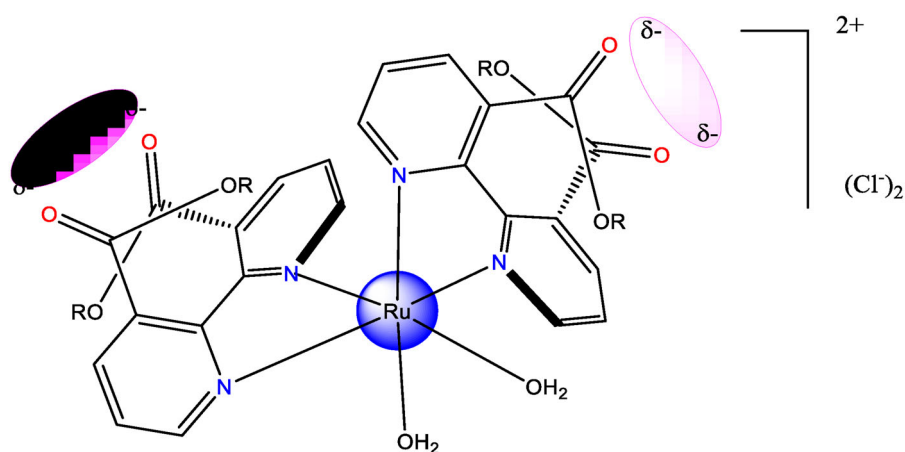


Figure 12. Organometallic approach of Prof Taibi BEN HADDA team as proposal to fight against COVID-19 by using Ruthenium (II) complexes of Polypyridines in presence of SATIVEX spray as Supplementary synergetic drug in goal to obtain immediate relaxation and more antiviral therapeutic effect.

In addition, the molecular electrostatic potential and the frontier molecular orbital of the title compound were further studied using DFT, indicating that the compound has certain nucleophilic reactivity and good chemical stability. The frontier molecule orbitals (FMOs), which refer to two frontier

molecular orbitals called HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) play a very important role in the reactional mechanisms. Molecular electronic and physicochemical properties such as ionization potential (Table 2), electron affinity, chemical

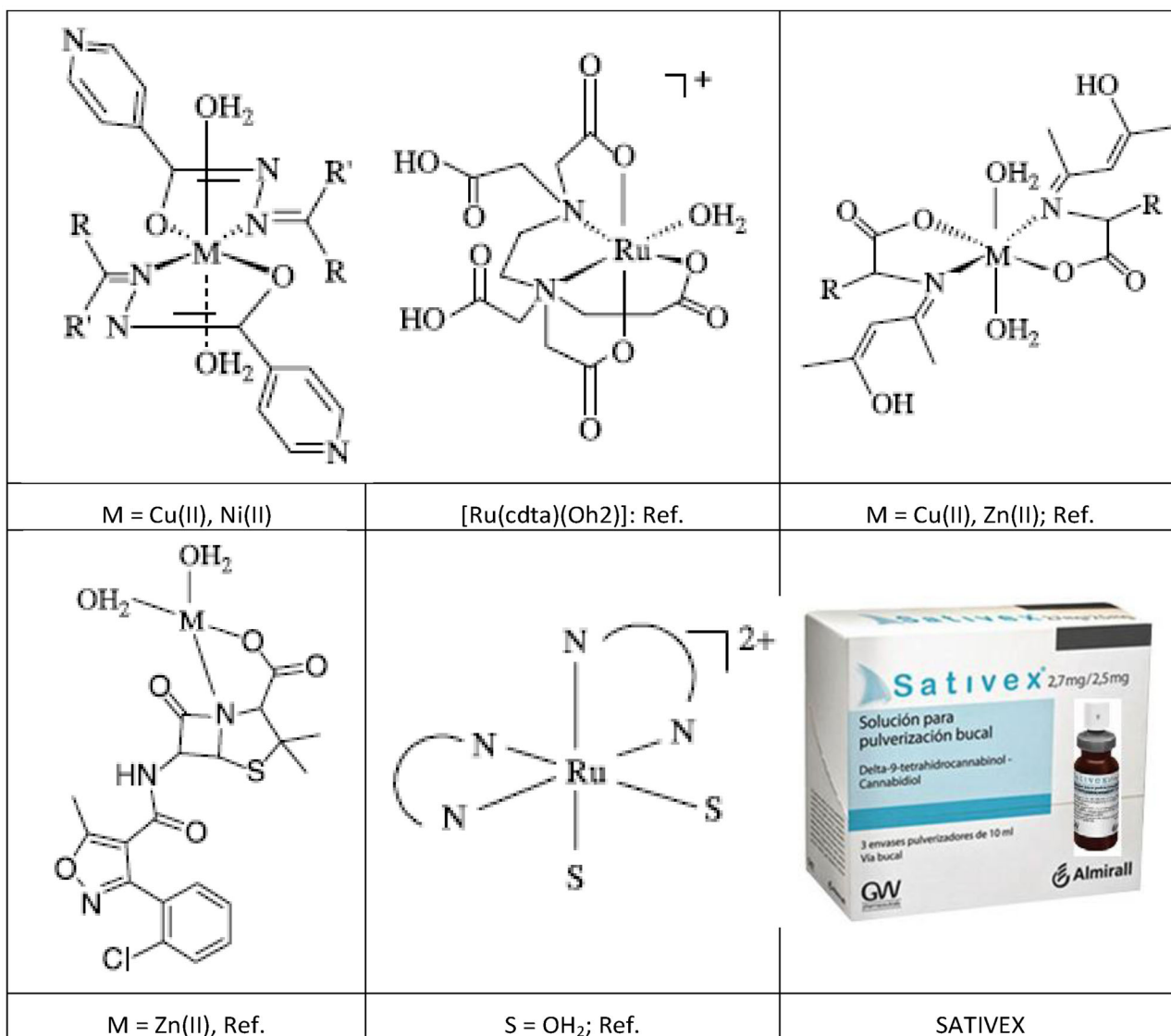


Figure 13. Molecular structure of some bioactive complexes bearing [Metal(OH₂)₂] moiety and pharmaceutical SATIVEX drug (<https://sweetseeds.es/fr/sativex-med-icamento-con-extractos-de-marihuana-ya-en-espana/#>).

reactivity, kinetic stability, electronegativity, and electrophilicity (Parr & Pearson, 1983), are a chemical property that informs us about the stability of the molecule.

In the present investigations, the energy gap of hydroxychloroquine is 4.5079 eV. A small energy gap of HOMO-LUMO means more chemical active and low kinetic stability. The other parameters like ionisation potential (I), electron affinity (A), chemical potential (μ), global hardness (η), global softness (S), electronegativity (χ) and electrophilicity index (ω) of title molecule are computed by using HOMO and LUMO energy values.

The electrophilicity index helps in describing the biological activity of the molecule, ($\omega = 2.5903$) for hydroxychloroquine.

3.3. Frontier molecular orbitals (FMOs)

To investigate the chemical stability of conformer 8, the energies of the highest occupied molecular orbital (E_{HOMO}), the lowest unoccupied molecular orbital (E_{LUMO}), and their orbital energy gap (ΔE) were calculated using the B3LYP/6-

31G (d) method. The pictorial illustration of the FMOs and their respective positive and negative regions represented by red and green colors are shown in Figure 4. The values of E_{HOMO} and E_{LUMO} are -6.0790 eV and -1.2438 eV respectively and the value of the energy separation between the HOMO and LUMO is 4.8352 eV for the most stable conformer. The large HOMO-LUMO energy gap means high excitation energy of the excited state, good chemical stability and large hardness for the calculated conformer.

3.4. Molecular electrostatic potential

Electrostatic potential maps give information on the molecular regions preferred by an electrophile or a nucleophile. Any chemical system creates an electrostatic potential around itself (Murray & Sen, 1996). The different electrostatic potentials at the surface of the molecule are represented by different colors. Electrostatic potentials increase in red < orange < yellow < green < blue, and red indicates the electron-rich region and blue indicate the electron deficient

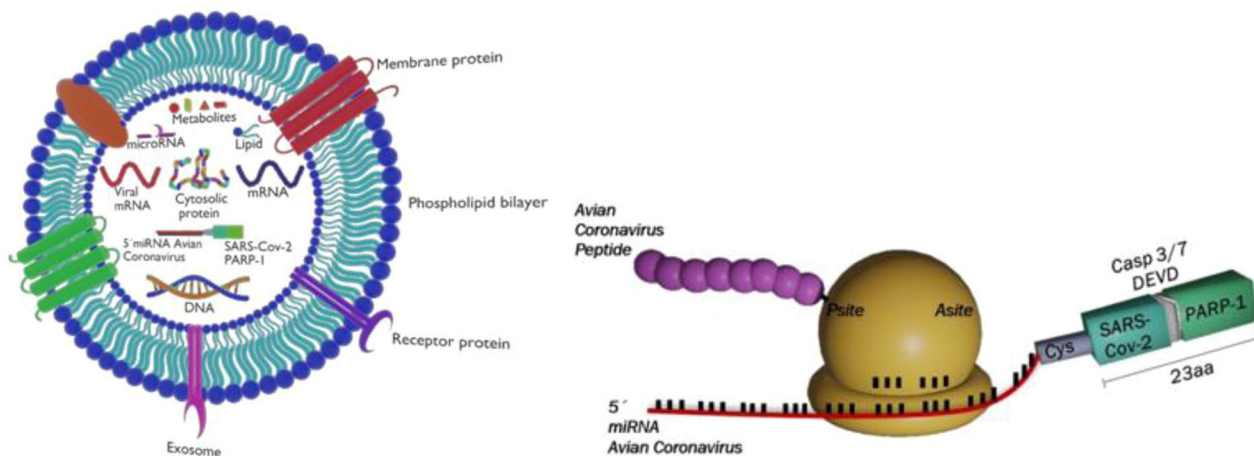


Figure 14. Exosomes as potential biomarkers of vaccination.

region. Figure 5 shows phosphonate groups and the N atoms of the conformational isomer and is surrounded by negative charges, indicating some possible nucleophilic attack sites. Besides, the positive charge regions are located on the H atoms on the rings.

The Mulliken charge calculations (Table 3) indicate the presence of the antiviral *O,O*-pharmacophore site with $O^{\delta-}/O^{\delta-}$, as it was postulated based on fundamental concepts of POM Theory.

3.5. Docking study of remdesivir

Remdesivir exhibited high potential for the binding to the COVID-19 M^{pro} . The best pose (pose 9) of inhibitor achieved the total energy value (-146.197 kcal/mol) of which the van der Waals forces participate with 109.165 kcal/mol, while the hydrogen bonds with 38.032 kcal/mol. Energies of the main interactions between COVID-19 M^{pro} and remdesivir are presented in Table 4.

Figure 6 shows the docking and interactions of remdesivir at the N3-binding site of COVID-19 M^{pro} .

The binding site of COVID-19 M^{pro} was defined according to the binding mode of synthetic glutamine analogs N3 as an inhibitor (PDB ID: 6LU7). The substrate-binding pocket is located in a cleft between domain I (residues 8–100), and domain II (residues 101–183) and it is composed of Cys144 and His41 (Figures 7 and 8). Remdesivir forms two strong hydrogen bonds: one between the nitrogen atom from triazine ring and Thr24, and second with hydroxyl group from dihydroxyoxolan group and Ser46. Other hydrogen bonds formed amino nitrogen atom and propanoate oxygen atom with Thr25, Thr45, Gly143, Ser144, Cys145. The strongest van der Waals interactions are formed with Asn142. Aminopyrrole ring forms amide- π interactions with Met 49. Inhibitor N3 in complex with human coronavirus HCoV-NL63 M^{pro} forms standards covalent bonds with Cys144, similar to hydrogen bonds with Cys 145 in complex COVID-19 M^{pro} and remdesivir (Wang et al., 2016). The hydrogen bond between the lactam oxygen of N3 and His163 could be compared with van der Waals interaction with His164. The docking study indicated that remdesivir exhibited high potential

for binding to the active site of COVID-19 M^{pro} and could be potential therapeutic agents in COVID-19 infections.

3.6. POM analyses and identification of pharmacophore sites

POM physicochemical analysis or ADME/T is important to qualify drugs and their efficacy as leading candidates against various biotargets, as like antibacterial (Grib et al., 2020; Hatzade et al., 2015; Jamalis et al., 2020; Jarrahpour et al., 2019; Mabkhot et al., 2015, 2016; Messali et al., 2014, 2015; Nasruddin et al., 2018; Rad et al., 2017; Rbaa et al., 2019; Sajid et al., 2016; Tatar et al., 2016), antifungal (Al-Maqtari et al., 2017; Khan et al., 2017; Rachedi et al., 2020; Radi et al., 2015; Tighadouni et al., 2016; Titi et al., 2019), antiviral (Chander et al., 2017; Lahsani et al., 2015), antitumoral (Bechlem et al., 2020; Kamal et al., 2019; Piaz et al., 2018; Rachedi et al., 2019, 2020; Youssoufi et al., 2015), antiparasitic drugs and various enzymes inhibitors (Amirkhanov et al., 2019; Ben Hadda et al., 2018, 2020; Mabkhot et al., 2014; Rauf et al., 2017).

The POM physicochemical calculations included a partition coefficient ($cLogP$), aqueous solubility, donor hydrogen bond, and drug-likeness, evaluated in terms of Lipinski's rule-of-five. To qualify oral bioavailability, the topological polar surface (TPSA) should be $<140 \text{ \AA}^2$. The results of POM physicochemical analyses of compounds are shown in (Figure 9), and these compounds showed good oral bioavailability ($cLogP$ range = $0.31-3.08$). Drug Score (DS) and Drug Likeness (DL) analyses were also within the required limits. The comparison data is shown in (Tables 5 and 6).

3.7. Mechanistic study: How each drug works?

The total atom charge calculations of remdesivir (Figure 10) indicate clearly the antiviral *O,O*-pharmacophore site with $cis-O^{\delta-}/O^{\delta-}$, as it was exactly confirmed above by Mulliken charge calculations of optimized conformer. On the other hand, when we inspect the molecular structure of hydroxy-chloroquine, we do not found any one of the antiviral *cis-O,O* or *cis-N,O* or *cis-N,N*-pharmacophore sites. The N,OH is

classified as an antibacterial pharmacophore site as it was always postulated by POM Theory. So its mechanism of interaction with coronavirus should be different. In fact, Nsp2 of heterocyclic ring constitutes an excellent center of ligation of transition metals (Figure 11). The presence of ZnSO₄ in the American treatment is of crucial role because its presence with hydroxychloroquine as potential monodentate N-ligand should lead us to the formation of the complex below, bearing two optional therapeutic functions (Figure 12).

All complexes bearing [M-(OH)₂]₂ moiety are of great importance in modern medicinal chemistry. Many such selected metal-based compounds contain [M-(OH)_n], [M-(OH)_n], [M=O], which have shown interesting and potential anti-tumor or antibacterial activity (Ben Hadda et al., 2009, 2015; Chatterjee et al., 2006; Chohan et al., 2006; Chohan & Supuranm, 2006) (Figure 13). Bipyridyl-derived ruthenium(II) complexes with antimycobacterial *in vitro* have been reported with our group. The ruthenium(II) complex of Bpy* also showed important activity (%Inhibition = 100%; MIC < 6.5 µg/mL). In another report, a ruthenium(II) complex displayed a fantastic anti-tumor activity with MIC 18,000-fold lower than that of Staurosporine derivative (<https://grantome.com/grant/NIH/R01-GM071695-04>).

For the reason cited above, we can propose some ruthenium(II) complexes as a potential perspective to fight with COVID-19 with success (Figure 13).

4. Conclusion

In this study, three proposed anti-COVID-19 supportive drugs/treatments (Remdesivir, Hydroxychloroquine, Azithromycin) have been analysed, and their pharmacophore sites are characterized via bioinformatic DFT, docking and POM analysis. *Osiris* calculations of analysed compounds reveal that hydroxychloroquine and azithromycin are the safest ones. The most important antiviral activities of hydroxychloroquine and azithromycin agree with the POM results obtained and the tested hydroxychloroquine compound via a redox mechanism.

The addition of zinc sulfate to hydroxychloroquine in the presence of azithromycin is far away from being innocent. The addition of ZnSO₄ can play various roles in the coordination of ligands and template effect. It should generate 'in situ' important Zn(II) complexes of hydroxychloroquine bearing [Zn(H₂O)₂]₂ moiety, source of redox properties, and an antibacterial N,OH-pharmacophore site. For these reasons, the hypothetic resulting complex *cis*-diaquo-Zn-hydroxychloroquine is efficient against coronavirus and should be tested against opportunistic bacteria and other viruses.

Now, it is clear that the Zn(II) is well involved in antiviral activity via the *in situ* formation of [(Zn(Hydroxychloroquine)₂(H₂O)₂]₂ complex. So this is encouraging to prepare and test similar complexes of ruthenium(II) against coronavirus. The ruthenium(II) complexes are more stable and safe.

5. Perspectives

- Identification of a miRNA-peptide with theoretical Exosome Affinity according to COVID-19 structure using

Exosomes as potential biomarkers of vaccination (Figure 14) (Cruz-Rodriguez et al., 2020).

- Synthesis and validation of an effective vaccine, allowing prevention against COVID (Cruz-Rodriguez et al., 2020).
- Clinical trials of the candidate vaccine, using the Food and Drug Administration (FDA) protocols.

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Disclosure statement

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