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ORIGINAL RESEARCH

A computational study of potential therapeutics for COVID-19 invoking conceptual density functional theory

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Abstract

The pandemic, COVID-19, has caused social and economic disruption at a larger pace all over the world. Identification of an effective drug for the deadliest disease is still an exigency. One of the most promising approaches to combat the lethal disease is use of repurposed drugs. This study provides insights into some of the potential repurposed drugs viz. camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir in terms of the computational quantum chemical method. Properties of these compounds have been elucidated in terms of Conceptual Density Functional Theory (CDFT)-based descriptors, IR spectra, and thermochemical properties. Computed results specify that hydroxychloroquine is the most reactive drug among them. Thermochemical data reveals that camostat mesylate has the utmost heat capacity, entropy, and thermal energy. Our findings indicate that camostat mesylate and hydroxychloroquine may be investigated further as potential COVID-19 therapeutics. We anticipate that the current study will aid the scientific community to design and develop viable therapeutics against COVID-19.

Keywords COVID-19 · Repurposed drug · CDFT · Camostat mesylate · Hydroxychloroquine · HOMO–LUMO

Introduction

The outbreak of the virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has caused a catastrophic loss of human lives. An abrupt disruption to healthcare has raised several challenges to the system worldwide. The first case with acute respiratory sickness was detected in the Hubei province of China on November 17, 2019 [1]. On January 07, 2020 Chinese authorities substantiated that virus is novel and belongs to the coronavirus family, the origin of which is unknown. Later, on January 30, 2020 WHO declared a public health emergency and named this disease as COVID-19. It is basically positive single-stranded large RNA that affects humans as well as animals. The term Coronavirus was coined by Tyrell and Bynoe in 1966, and it was mainly observed in patients having colds [2]. It causes upper respiratory tract infections in humans ranging from mild to moderate. As per the report, till July 18, 2022, there have been 567,857,253 confirmed cases and a total of 6,387,812 deaths reported globally due to COVID-19. Several clinical trials and mechanisms are still under process to find the suitable remedial drug of COVID-19 [3]. In the absence of dedicated drug, several countries have given permission to use of repurpose drug for the treatment of COVID-19 patients [4–12]. Since drug repurposing is the cost-effective and has a rapid development cycle, it has emerged as a viable technique and is of great interest [13]. The term drug repurposing, also known as reprofiling, repositioning, or re-tasking, refers to the process of identifying novel therapeutic use for already existing drugs.

Repurposed drugs like quinine, chloroquine, lopinavir, ritonavir, camostat mesyalate, tenofovir, ribavirin, remdesivir, sofosbuvir, galidesivir, setrobuvir, anthracyclines-doxorubicin, epirubicin, idarubicin, daunorubicin hydroxychloroquine, nitazoxanide, and oseltamivir are used for the treatment of patients of COVID-19 [4–12, 14–18]. Ramkumar et al. [19] investigated drug tenofovir with the

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help of experimental as well as computational approach and observed nice correlation among atomic charge and chemical shift. Kaur et al. [20] reported the anti-parasitic drug ivermectin, which also has antiviral effects, may be used to treat COVID-19. The effectiveness of prospective drugs—ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir—for the treatment of COVID-19 is reported by Elfiky et al. [14]. Furthermore, authors also specified the significance of guanosine derivative, setrobuvir, and YAK against SARS-CoV-2. Wang et al. [21] stated that chloroquine and its derivative, hydroxychloroquine, which are used for the treatment of malaria patients are effective against COVID-19. Hydroxychloroquine is basically an antimalarial drug, considered an immune modulator [21]. It is used for the treatment of various diseases like malaria, systematic lupus erythematosus, and rheumatoid arthritis for a long time [22]. It is also known to be used in the treatment of COVID-19 alone and in combination with azithromycin. Several other possible combinations of hydroxychloroquine have been tested with other FDA-approved drugs that could be considered a promising treatment for COVID-19 [23]. It is similar to chloroquine in terms of chemical structure; however, it is reported that hydroxychloroquine has a lower toxicity index compared to chloroquine [24]. Hydroxychloroquine is known to possess immunosuppressive properties [25] which are reliable in reducing cytokine storm in case of severe COVID-19 [26]. Studies suggest that it can inhibit the replication of SARS-CoV-2 in vitro; in addition to this, hydroxychloroquine is also responsible for reducing the synthesis of sialic acid by inhibiting quinine reductase-2 [27]. Singh et al. [28] reported that chloroquine and its derivative hydroxychloroquine drugs are potential inhibitors for COVID-19. Tan et al. [29] stated that hydroxychloroquine is a potential drug for the treatment of COVID-19 patients. Roy et al. [30] reported that hydroxychloroquine exhibits stronger affinity against the major proteolytic of COVID-19. They found docking value of hydroxychloroquine as − 6.300 kcal/mol.

According to the in vitro human cell and animal research, camostat mesylate suppresses virus-cell membrane fusion and subsequently viral reproduction. Breining et al. [31] stated that powerful TMPRSS2 agent known as camostat mesylate has a good safety profile, which is administered orally, and decreases the viral load during the treatment of severe infectious disease in mice. Authors also reported that as it is a potential antimicrobial agent and helps to reduce viral load in patients; this drug can be effective against COVID-19. It is observed that camostat mesylate restricts the growth and pathology of SARS-CoV and anticipated that it will show similar impact on MERS-CoV [32–34]. Gunst et al. [35] studied the effect of camostat mesylate in COVID-19 patients and found that camostat mesylate would stop SARS-CoV-2 growth and reduced the possibility of hyper-inflammation and inhibit the infection. Ramakrishnan et al. [36] studied the molecular docking and molecular dynamics simulations of repurposed leupeptin, camostat, and nafamostat against SARS-CoV-2 and found docking score of camostat as − 6.648 kcal/mol.

In vitro virus growth and high throughput screening have recently led to the identification of nitazoxanide as a potential treatment for SARS-CoV-2 [21, 37–40]. Nitazoxanide actively acts against a range of organisms, such as viruses, bacteria, protozoa, and helminths. It is known to suppress the production of many pro-inflammatory cytokines in peripheral blood mononuclear cells including IL-6, IL-8, and TNF-α [41, 42]. Nitazoxanide is found effective and economical with good safety profile for the treatment of COVID-19 disease [43]. Rossignol et al. [40] reported that nitazoxanide is well-tolerated and safe to use in line with its well-known safety profile. After clinical trials, authors found that early nitazoxanide administration may slow the development of severe disease in elevated patients and enhance the initiation of a sustained treatment improvement in patients with asymptomatic infection. Due to its in vitro low IC_{50} towards SARS-CoV-2, nitazoxanide shows tremendous potential. It has the ability to obstruct SARS-CoV-2 entry and impede its proliferation. In addition to reducing the cytokine storm, nitazoxanide helps to improve the patient immune system. It is reported that use of nitazoxanide suggests a potential for lung safeguard and the avoidance of multiple organ dysfunction [44]. Authors also stated that nitazoxanide may have health efficacy for people suffering from COVID-19 as well as also have some other disease [44]. Calderon et al. [45] investigated efficacy of hydroxychloroquine and hydroxychloroquine plus nitazoxanide in COVID-19 patients. They anticipated that combination of hydroxychloroquine and nitazoxanide will be superior than hydroxychloroquine towards COVID-19.

Oseltamivir (Tamiflu) is a neuraminidase inhibitor approved in 1999 by FDA [46]. It is effective against influenza A and influenza B [47, 48]. Zhang et al. [49] stated that neuraminidase can be effective against SARS-CoV, due to the similarity found between the SARS protein Spike (S) 1 site and neuraminidase. It is reported that oseltamivir in combination with other drugs like favipiravir, oseltamivir, and ribavirin is effective against influenza H1N1 [50, 51]. In comparison to other antiviral drug officially approved for COVID-19 treatment, remedesivir is administered intravenously. However, oseltamivir is ingested as an oral prodrug (oseltamivir phosphate), and it is available in the form of liquid suspension or as a pill, and can be used off-label for the treatment. It gets converted to its active form, oseltamivir carboxylate, by the hepatic esterases [52]. Moreover, it is nonexpensive while remdesivir is costlier and becomes a topic of discussion

when prescribed to patients with mild symptoms in the early days of disease [53]. Oseltamivir is economical and has a predictable linear pharmacokinetic profile and has been proven safe for almost all age brackets [53, 54]. Coenen et al. [55] reported that oseltamivir combined to standard care helped patients suffering from coronavirus (excluding SARS-CoV-2) to cure more quickly than standard care alone. The probable mechanism of action for this drug includes the inhibition of viral neuraminidase and the possible correlation predicted to be helpful in treatment against COVID-19 is the virus exocytosis inhibition [56]. Muralidharan et al. [57] reported that oseltamivir in combination with lopinavir and ritonavir is very potent against SARS-CoV-2 protease. Zendehdel et al. [58] reported that patients with COVID-19 who received oseltamivir treatment in the first few hours following hospitalization resulted in speedy recovery and lesser fatality rate. Mitja et al. [59] stated that people who are at high infection risk before or after exposure to disease outbreak can take oseltamivir, according to the WHO [60]. After clinical trials Chiba et al. [61] reported that oseltamivir treatment combined with antibiotic therapy may decrease the duration of fever in COVID-19 patients. Belhassan et al. [62] investigated the major proteolytic of the SARS-CoV-2 virus using N-substituted oseltamivir variants. Tan et al. [29] reported that patients administered with oseltamivir has considerably lower hospital stay duration as compared to patients administered to the arbidol, corticosteroid, and lopinavir/ritonavir.

Therefore, study of repurposed drugs—camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir—are of interest. Recently, the use of computational tools in addition to in silico studies has become quite popular, since it discerns a drug's quantum chemical properties efficiently [63, 64]. Herein, we are providing insights into the repurposed drugs—camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir—by using semi-empirical approach. Conceptual Density Functional Theory (CDFT)-based global descriptors—HOMO (highest occupied)-LUMO energy gap, electronegativity, chemical hardness, softness, electrophilicity index, and dipole moment of these repurposed drugs—are computed and analyzed. HOMO and LUMO are important factors to study the reactivity of molecules. The highest energy orbital, HOMO, is populated with electrons, making it an electron donor, whereas, the lowest energy orbital, LUMO, has capacity for electrons to enter, making it an electron acceptor [65]. Significant studies have been performed in recent years to compute HOMO- LUMO, IR and different physico-chemical properties of potential inhibitors of COVID-19 by using DFT technique, which is useful in elucidating structure properties and predicting biological activity [18, 30, 66–70].

Computational details

DFT studies, which have gained enormous admiration, are helpful in predicting the electronic properties of various atoms, molecules, and even compounds with complex structures [71]. The computation of all the repurposed drugs is carried out using Gaussian 16 software [72]. Chemdraw structure of repurposed drugs—camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir—are presented in the Fig. 1. Geometry optimization of these species is performed via a quantum chemical semi-empirical approach with PM6 exchange–correlation functional. The relative importance and efficacy of the semi-empirical method in drug design have been elaborated in previous studies [73–76], and same approach is applied to COVID-19 drugs in recent studies [77, 78].

With the help of FMOs (frontier molecular orbitals), various reactivity descriptors of repurposed drugs—camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir—are calculated as under [71]:

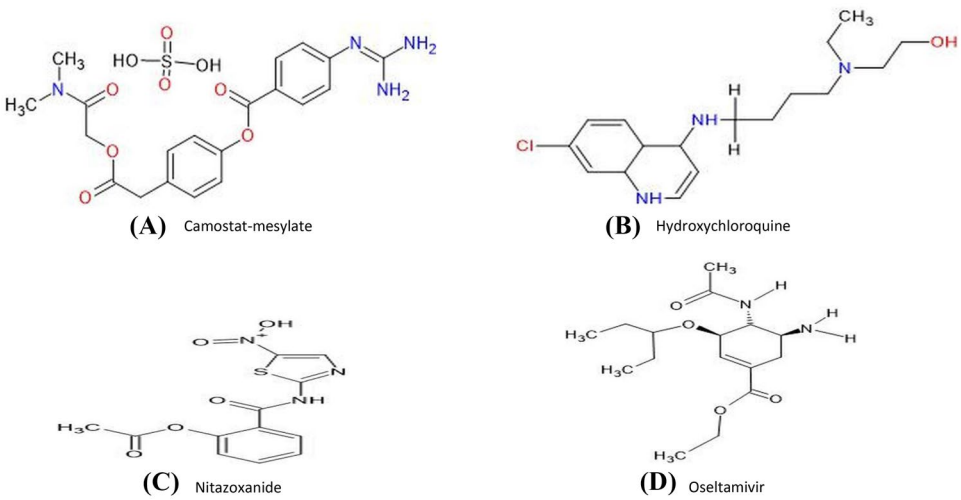

Fig. 1 Structures of investigated compounds

$$I = -\mathrm{E_{HOMO}} \quad (1)$$

$$A = -\mathrm{E_{LUMO}} \quad (2)$$

where "*I*" is the ionization potential and "*A*" refers to electron affinity

$$\text{Electronegativity; } \chi = -\mu = \frac{I + A}{2} \quad (3)$$

$$\text{Chemical hardness; } \eta = \frac{I - A}{2} \quad (4)$$

where μ is the chemical potential

$$\text{Chemical softness; } S = \frac{1}{2\eta} \quad (5)$$

$$\text{Chemical potential; } \mu = -\chi \quad (6)$$

$$\text{and electrophilicity index; } \omega = \frac{\mu^2}{2\eta} \quad (7)$$

Results and discussions

Conceptual density functional theory-based descriptors

Optimized structures of the repurposed drugs—camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir, as computed invoking a semi-empirical approach with PM6 exchange–correlation—are presented in Fig. 2. Physicochemical properties like optimization energy, ionization potential, electron affinity, HOMO, LUMO, HOMO–LUMO gap, electronegativity, hardness, softness, chemical potential, electrophilicity index, dipole moment, and polarizability of

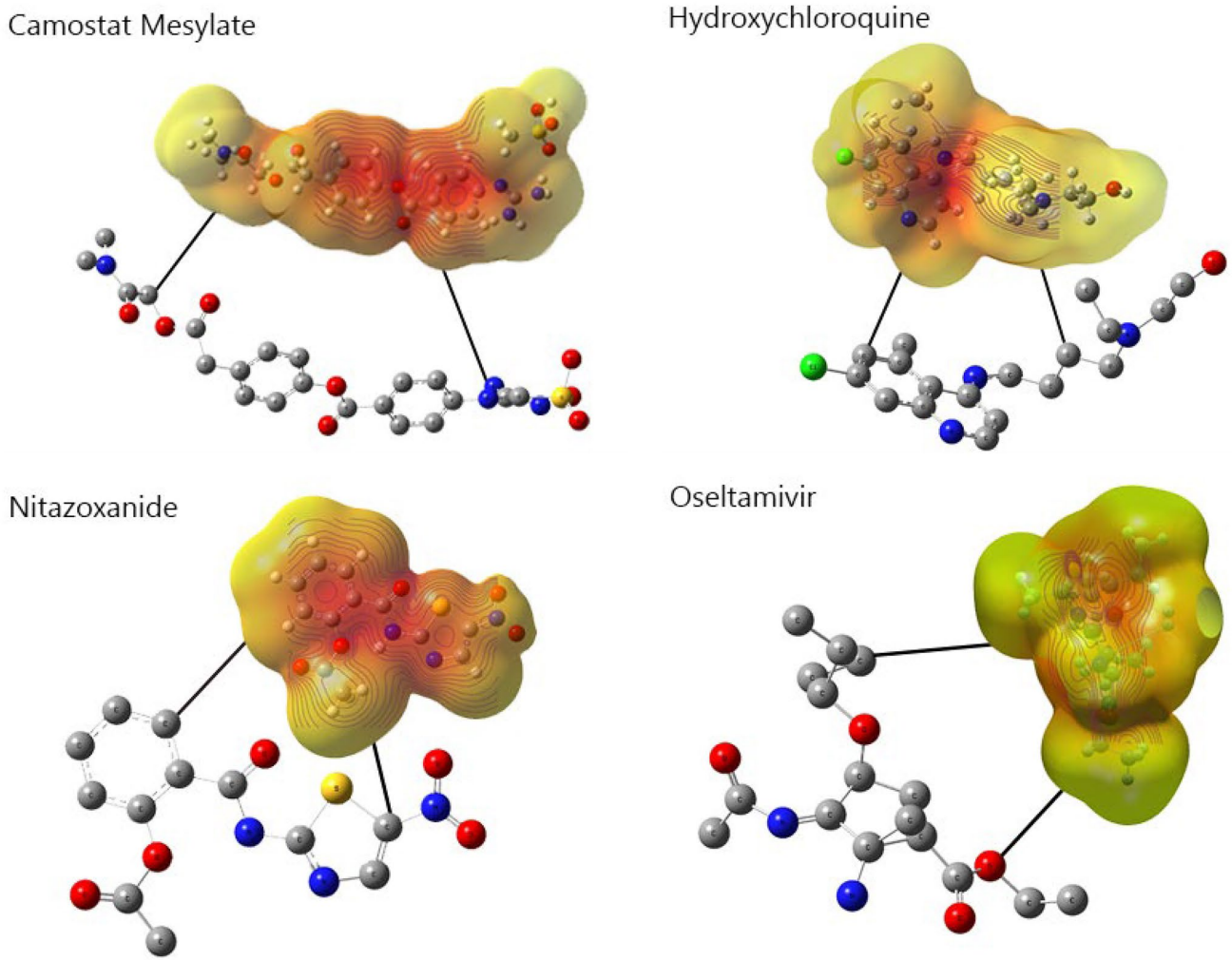

Fig. 2 Optimized geometries of compounds with visuals of ESP (electrostatic potential) surface areas

Table 1 Physico-chemical properties of camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir

Descriptors	Camostat mesylate	Hydroxychloroquine	Nitazoxanide	Oseltamivir
Optimization energy (eV)	−12.406	2.968	−3.328	−8.262
Ionization potential (eV)	9.058	6.193	9.568	9.428
Electron affinity (eV)	0.823	0.619	1.700	3.227
HOMO–LUMO gap (eV)	8.235	5.574	7.867	6.201
Electronegativity (eV)	4.941	3.406	5.634	6.328
Chemical hardness (eV)	4.118	2.787	3.934	3.101
Chemical softness (eV)	0.121	0.179	0.127	0.161
Chemical potential (eV)	−4.941	−3.406	−5.636	−6.328
Electrophilicity index (eV)	2.964	2.081	4.035	6.457
Dipole moment (Debye)	6.098	2.735	9.889	4.947
Polarizability (a.u.)	275.303	210.539	186.390	155.405

these repurposed drugs are calculated through Eqs. (1) to (7) and listed in Table 1. From the results, it is observed that camostat mesylate has the lowest optimization energy whereas hydroxychloroquine is showing the highest optimization energy among these compounds. The positive value for hydroxychloroquine can be attributed to its lesser stability compared to other compounds under study. Ionization potential (IP) and electron affinity (EA) values are calculated using Koopman's theory according to which IP is regarded as $-E_{HOMO}$ and EA are calculated as $-E_{LUMO}$ [79–81]. The values have been compiled in Table 1. It is also observed that hydroxychloroquine has the lowest IP and EA among other investigated molecules. IP and EA are useful in investigating optimal bioavailability and blood–brain permeation respectively according to reported studies [81–83].

It is important to study the behavior of frontier molecular orbitals in order to understand the reactivity and stability of molecules [84, 85]. This includes capturing the role of HOMO, which is present in the filled state, and LUMO, which is found to be empty. These parameters help to predict the chemical reactivity of any molecular species. The HOMO–LUMO gap refers to the excitation energy required for shifting an electron from HOMO to LUMO. It plays a significant role in the interaction of drugs with receptors. The larger the HOMO–LUMO gap, more excitation energy is needed for the electron transfer. Apart from this, a larger gap indicates the presence of hydrophilic interaction which is a sign of better bonding with receptors. In this study, hydroxychloroquine has the lowest HOMO–LUMO gap which means the HOMO and LUMO of this molecule are the closest compared to other systems as presented in this report, and hence excitation becomes easier in this case. A small energy gap indicates high chemical reactivity. Similarly, camostat

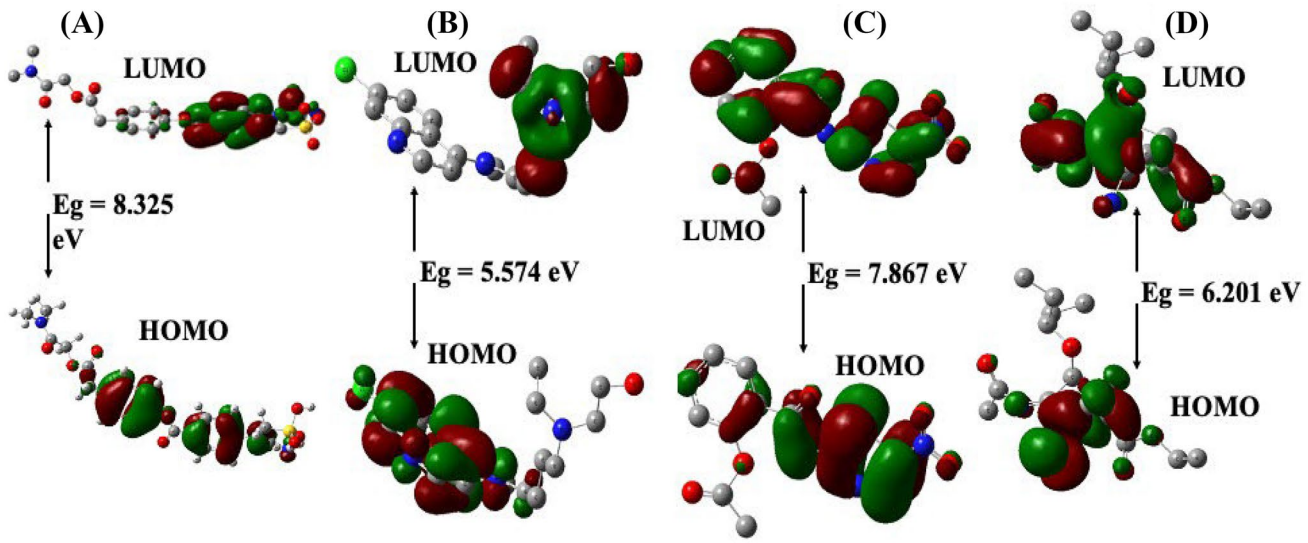

Fig. 3 HOMO and LUMO for **A** camostat mesylate, **B** hydroxychloroquine, **C** nitazoxanide **D** oseltamivir

mesylate exhibits the maximum HOMO–LUMO gap. It indicates that camostat mesylate is the most stable compound among these drugs. HOMO and LUMO orbitals of these systems are presented in Fig. 3. Furthermore, the Density Of States (DOS) of these drugs are obtained by using GaussSum software [86] and depicted in Fig. 4. The DOS spectra reflect the position of occupied and virtual orbitals. The spectra of these repurposed drugs are shown in the range of − 20 to 0 eV. The DOS spectra values are consistent with the energy difference between HOMO and LUMO for the ligands.

It is noticed that the HOMO–LUMO gaps of these drug molecules have correlation with CDFT-based descriptors. The electronegativity values of these molecules are in the range of 3.406 to 6.328 eV. Hydroxychloroquine shows the minimum value of electronegativity, whereas oseltamivir exhibits the maximum electronegativity value. The electronegativity value of hydroxychloroquine is in agreement with the previous value reported by Noureddine et al. [87]. The data from Table 1 reflects that the chemical hardness and softness of these molecules are having a direct and inverse relationship with the HOMO–LUMO gap respectively. The HOMO–LUMO gap and chemical hardness of these systems follow order as: hydroxychloroquine < oseltamivir < nitazoxanide < camostat mesylate. The chemical hardness of molecular species is also related to stability. Chemical hardness and softness are inversely related to each other. A system with the maximum value of hardness displays the lowest softness and vice-versa. It is reported that molecular species with low hardness exhibits the maximum reactivity [88, 89]. In this case, camostat mesylate has the maximum chemical hardness and the lowest softness, proving that this molecule is difficult to polarize and hence indicates its stability towards excitation.

Chemical potential deals with the escaping tendency of electrons involved in a stable system [90]. It is reported that with decreasing chemical potential, the reactivity of species tends to increase [90, 91]. Data reveals that hydroxychloroquine and oseltamivir display the largest and smallest value of chemical potential respectively. The computed value of hydroxychloroquine is in agreement with the previous value reported by Noureddine et al. [87].

The electrophilicity index is an important reactivity descriptor that plays a vital role in understanding the reactivity of chemical species as it refers to the capacity of a system to accept electrons [92]. A low value of the electrophilicity index suggests the good nucleophilicity of compound, while a high value is a sign of good electrophile in behavior. The electrophilicity index values of these repurposed drugs are found between 2.081 and 6.457 eV. Hydroxychloroquine exhibits a low value of electrophilicity index, whereas oseltamivir shows a high value.

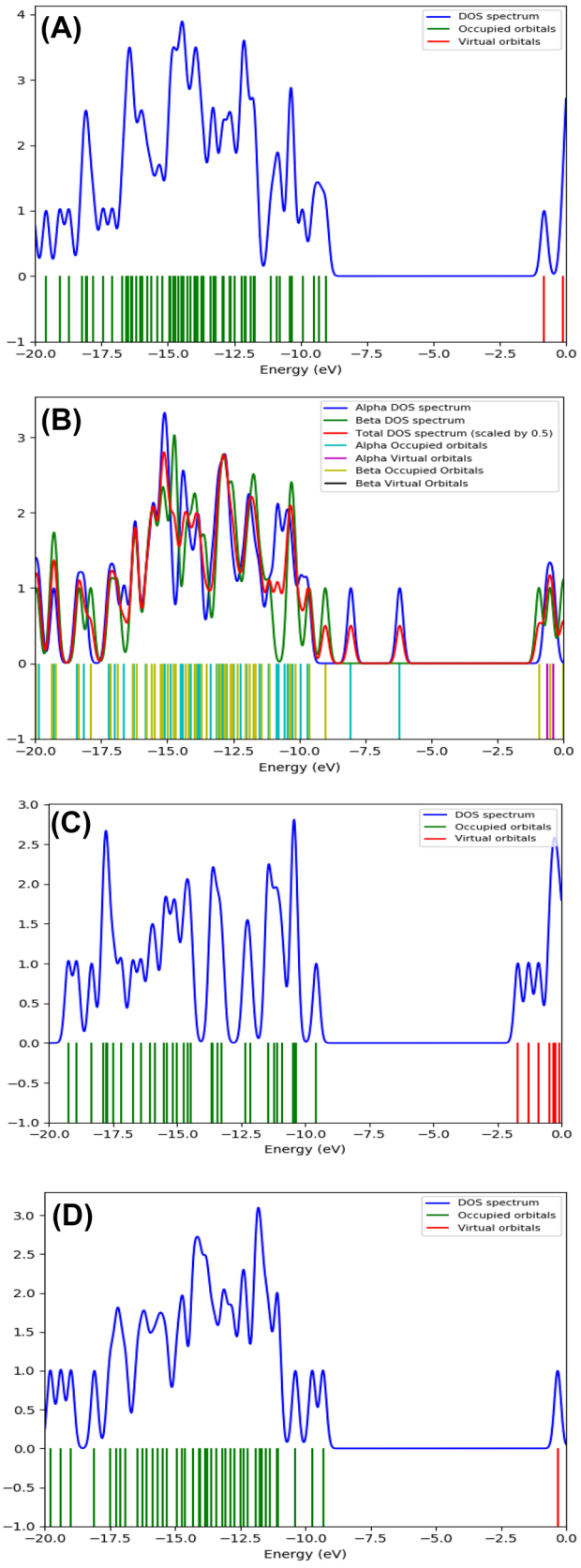

Fig. 4 Density of states for **A** camostat mesylate, **B** hydroxychloroquine, **C** nitazoxanide, **D** oseltamivir

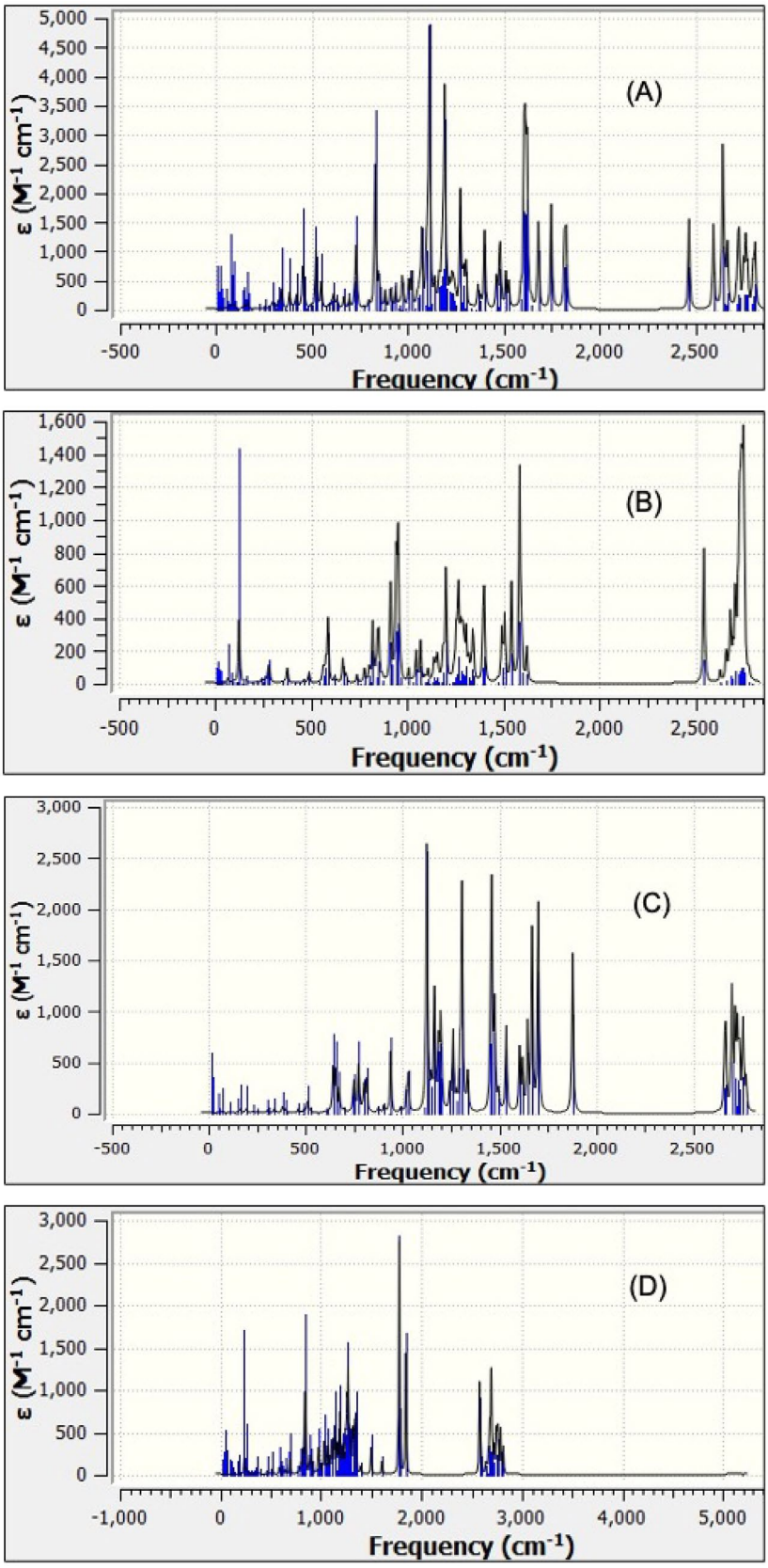

Fig. 5 IR activity for **A** camostat mesylate, **B** hydroxychloroquine, **C** nitazoxanide, **D** oseltamivir

Table 2 Heat capacity, entropy, and thermal energy

Species	Camostat mesylate	Hydroxychloroquine	Nitazoxanide	Oseltamivir
Heat capacity (cal/mol-K)	135.718	100.033	69.870	102.061
Entropy (cal/mol-K)	265.870	214.140	153.154	193.649
Thermal energy (Kcal/mol)	291.048	252.233	133.712	262.205

Dipole moment and polarizability obtained from chemical quantum calculations are also presented in Table 1. The dipole moments of these drugs are in the range of 2.735 to 9.889 Debye. It is observed that hydroxychloroquine and nitazoxanide offer the minimum and the maximum values of dipole moment respectively. The high value of dipole moment may indicate their binding position within a particular target protein [93]. The degree to which a charge influx affects the molecular system's electron cloud's resistance indicates how polarizable a substance is. Furthermore, it relies on the size of the molecules and the composition of the compounds [93]. The polarizabilities of these repurposed drugs are found between 155.045 and 275.303 a.u. Oseltamivir and camostat mesylate display the minimum and maximum polarizability respectively.

IR spectra

This section includes the IR activity of repurposed drugs—camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir. IR activity of these compounds is shown in Fig. 5. The vibrational frequencies for camostat mesylate are within the range of 1.741 to 1112.560 cm^{-1}. The maximum magnitude for IR is 1362.236 km/mole which is found at the highest vibrational frequency (1112.562 cm^{-1}), whereas the lowest IR intensity (0.065 km/mole) is obtained at 117.590 cm^{-1}. In the case of hydroxychloroquine, the frequency range is in between 4.061 and 2792.880 cm^{-1} and the lowest IR, i.e., 0.006 km/mole observed at 26.411 cm^{-1}. Meanwhile, the maximum IR activity of 239.132 km/mole is found at 2545.100 cm^{-1} for hydroxychloroquine. For nitazoxanide and oseltamivir, frequency ranges are between 14.390–1125.182 cm^{-1} and 18.164–5196.903 cm^{-1} respectively. It is observed that the highest IR value for nitazoxanide, i.e., 723.734 km/mole is obtained at the uppermost frequency (1125.182 cm^{-1}), while its lowest IR magnitude (0.020 km/mole) is at 59.800 cm^{-1}. Oseltamivir is having its lowest IR activity at the lowest frequency range, i.e., 0.166 km/mole at 18.164 cm^{-1}, and peak IR activity (670.246 km/mole) is found at 1779.752 cm^{-1}.

Thermochemical properties

Thermochemical properties like heat capacity, entropy, and thermal energy of these repurposed are calculated and listed in Table 2. Out of all the important thermodynamic variables as measured for proteins, heat capacity has the most complicated underpinning and the widest range of implications for protein folding and binding [93]. It imparts a temperature dependence on entropy, which will change their values and choose which of them will predominate. When an unfolding protein has a positive Cp, it achieves the maximum stability and frequently undergoes cold nucleation [93, 94]. It is noticed from Tables 1 and 2 that the drug camostat mesylate, with the minimum optimization energy and the maximum HOMO–LUMO energy gap, exhibits the maximum value of heat capacity, entropy, and thermal energy, whereas nitazoxanide possesses the lowest value of these thermochemical properties. It follows the similar trend as reported previously by Al-Janabi et al. [93] for COVID-19 inhibitors.

Conclusion

It is important to investigate the potential repurposed drug against the COVID-19 disease. Herein, we have studied some repurposed drugs namely camostat mesylate, hydroxychloroquine, nitazoxanide, and oseltamivir invoking a semi-empirical approach. It is observed that hydroxychloroquine shows the lowest IP, EA, HOMO–LUMO gap, hardness, electronegativity, electrophilicity index, and dipole moment, whereas it exhibits the largest value of optimization energy, softness, and chemical potential. Similarly, camostat mesylate offers the lowest optimization energy with a maximum HOMO–LUMO gap. Based on the reactivity parameters evaluated in this study, it can be concluded that hydroxychloroquine is the most reactive system, whereas camostat mesylate is the most stable system among these species. IR activity of these drugs is also reported. Thermochemical data shows that camostat mesylate possesses the maximum heat capacity, entropy, and thermal energy, whereas nitazoxanide displays the lowest value of these thermochemical properties. Previously, docking scores of hydroxychloroquine and camostat mesylate are reported as − 6.300 kcal/mol and − 6.648 kcal/mol respectively. On the basis of computational study and the pertaining results, it can be proposed that camostat mesylate and hydroxychloroquine have the potential for further exploration as potential therapeutic drugs against COVID-19.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by S. The first draft of the manuscript was written by S and DK. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

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