Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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In silico study of remdesivir with and without ionic liquids having different cations using DFT calculations and molecular docking

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ABSTRACT

The new coronavirus is trying best to kill the humanity with its highly infectious nature and its first infection was reported in 2019; later this infection was named as COVID-19. Health-care systems are still the using repurposing drugs to cure the patients from this infection. Remdesivir is found to have good potential to cure the patients from this infection and is being extensively used during the 1st and 2nd wave of COVID-19. Therefore, in the present work, authors have studied the interaction of remdesivir with different ionic liquids with change in cations using density functional theory calculation in gaseous and water. Based on the DFT calculations, it was found that remdesivir interacts effectively with different ionic liquids based on the energy; further, the change in free energy for Remdesivir-[Bet-ester][Lev] (1) was found to be −3223.5758 and −3223.6533 hartree per particle in gaseous and water respectively and most stable; further, 2 and 3 have the comparable free energies. Further, the potential of remdesivir with and without ionic liquids against the main protease of SARS-CoV-2 was investigated using molecular docking. Results revealed that Remdesivir-[Chol][Lev] (2) and Remdesivir-[Chol-ether][Lev] (3) have shown promising results with binding energy of −129.64 kcal/mol and −125.44 kcal/mol respectively while Remdesivir [Bet-ester][Lev] (1) have a binding energy of -123.86 kcal/mol. It is important to mention that changing the cations in ionic liquid play an important role in the docking. It is also observed that the ionic liquid having sodium as cation, then the binding energy against Mpro of CoV is poor and even less than the remdesivir alone.

1. Introduction

The world has faced the threat of the several viral attacks in past and they have taken the lives of millions. The recent new coronavirus attack has endangered the humanity and is often referred to as COVID-19 by World Health Organization. A continuous fever, chest-pain, cough, pneumonitis patches in lungs causes difficulty in breathing and are some of the common symptoms of the infection due to new coronavirus [1–4]. The intensity and progress of this disease can be correlated with host immunological dysregulation. The advancement of novel drugs should be economically expensive and time taking against the new coronavirus and virus after the mutation in due course of time, that ultimately reduce the efficiency of medications partially or completely [5–8]. The world has faced the 1st and 2nd wave of infection due to coronavirus and start experiencing the 3rd wave due to mutation (omicron) in new coronavirus. It has also reported that OMICRONmay infect the vaccinated people at a higher rate. In the previous two waves, repurposing drugs were used to cure the symptoms of this infection and could be synthesized in huge quantity, a potential alternative candidate to deal with this situation.

Repurposing drugs are of considerable importance in curing patients suffering from the infection of SARS-CoV-2. Remdesivir has been used in the treatment of various viral infections like Ebola Virus, severe acute respiratory syndrome (SARS), Marburg Marburg virus, Middle East respiratory syndrome (MERS) and others. Drug repurposing reduces the cost and can be developed or synthesized in less time. It involves repurposing of antivirals to inhibit the protease activity and inhibit the RNA synthesis of the virus [9–11]. Remdesivir restrict reverse transcription and has potential for the inhibition of SARS-CoV-2. Remdesivir was extensively

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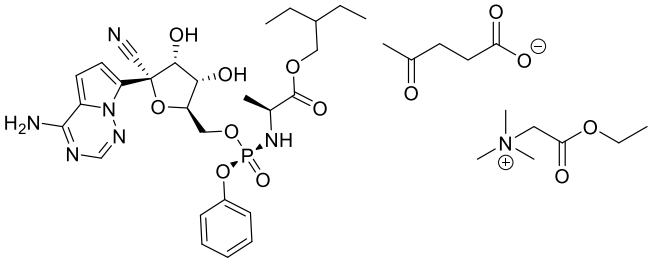
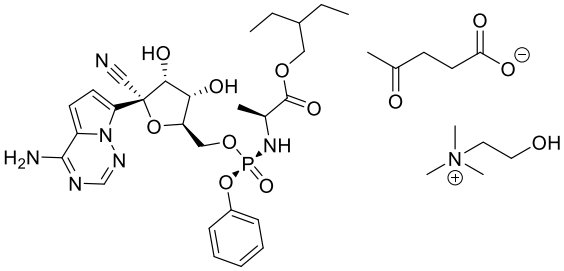
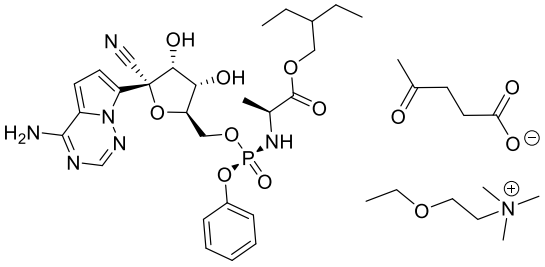
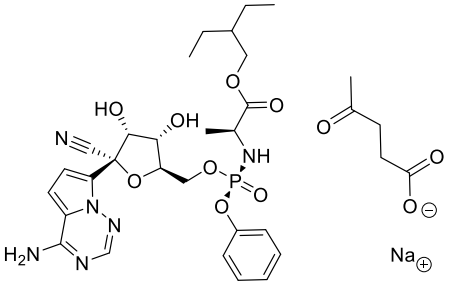
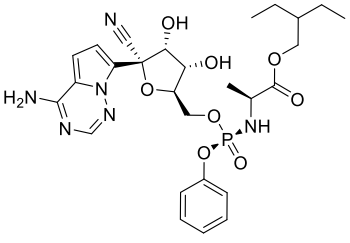
used in many countries during the second wave of infection due to new coronavirus [7,12–15]. There is a need to investigate the electronic structure of remdesivir and can be done by density functional theory (DFT) calculations using various computational tools [16–20]. Electronic structures of the compounds can be investigated in different solvents and different temperatures. It provides the enthalpy, free energy, dipole moment, different spectral studies to know about the structural and electronic behaviour of the compounds [21–24].

Ionic liquids (ILs) are highly demanded chemical entities in the academic institutions and industries as they are cost-effective, easy to synthesize, reused and have the ability to increase the activity of biological potential molecules [25–29]. They are explored for the protein stabilization, solubilize biomolecules and chemical entities, catalysis, conducting, enzyme extraction and others. Researchers are working on the use of repurposing drugs against the symptoms of the new coronavirus infection, therefore, remdesivir played promising role in this direction [30]. Further, it is reported that the synergistic effect of drugs showed better results than the individual one. Therefore, there is a need to understand the impact of ionic liquids on the structural and biological potential of remdesivir [31]. Research have explored the interaction of ionic liquids with small molecules using DFT calculations and investigate the impact of ionic liquids on the potential of small molecules for the inhibition of proteases. Even, ILs can be used as a potential antiviral agents against the main protease of SARS-CoV-2. Further, impact of ILs

Table 1
Structure of the remdesivir with and without ionic liquids having different cations.

Compound No.	Name of the compound	Structure of the compound
1	Remdesivir [Bet-ester][Lev]	
2	Remdesivir [Chol][Lev]	
3	Remdesivir [Chol-ether][Lev]	
4	Remdesivir Na	
5	Remdesivir	

on the acyclovir/ganciclovir against the Mpro of nCoV is studied using molecules docking [30,32].

In the present work, authors have focused on the investigation of thermodynamic stability of remdesivir with and without various ionic liquids (ILs) having different cations using Gaussian 16. Further, a synergistic effect of the remdesivir with different ILs against the main protease (Mpro) of new coronavirus (nCoV) has been investigated using molecular docking.

2. Computational calculations

2.1. Designing of the remdesivir and its combinations with ionic liquids

Authors have designed remdesivir and its combination with four ionic liquids were drawn using chemdraw as in Table 1 to investigate their stability as well as the synergistic effect of remdesivir and ILs against the main protease of SARS-CoV-2 [33].

2.2. DFT calculations

DFT calculations of the remdesivir with and without ionic liquids (1–5) as in Table 1 were performed on applying optimization + frequency, B3LYP-DFT-6311-G using Gaussian 16.0 in default as well as in water [21,34–37]. Various frontier molecular orbitals like highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) as well the optimized geometry for (1–5) were determined in gaseous and water to understand the localization of the electron density for determining the nucleophilic and electrophilic sites (Fig. 1) [38–41].

2.3. Thermodynamics parameter

Various thermodynamics parameters (zero-point energy, thermal energy, thermal enthalpy and thermal free energy) of the 1–5 were determined using DFT calculations as in (Table 2). Further, the optimization energy and dipole moment of 1–5 were also determined to understand the arrangement of atoms and solubility in water. Dipole moment of any system or molecule may be used to understand the polar character. If a molecular has high dipole moment indicate more polarity or difference in charge density; therefore, will be soluble in water. These data are used to understand the interaction of remdesivir with and without ionic liquids having different cations in gaseous state and water. It tells about the variation of the stability and solubility of remdesivir in the presence of ionic liquids with different cations.

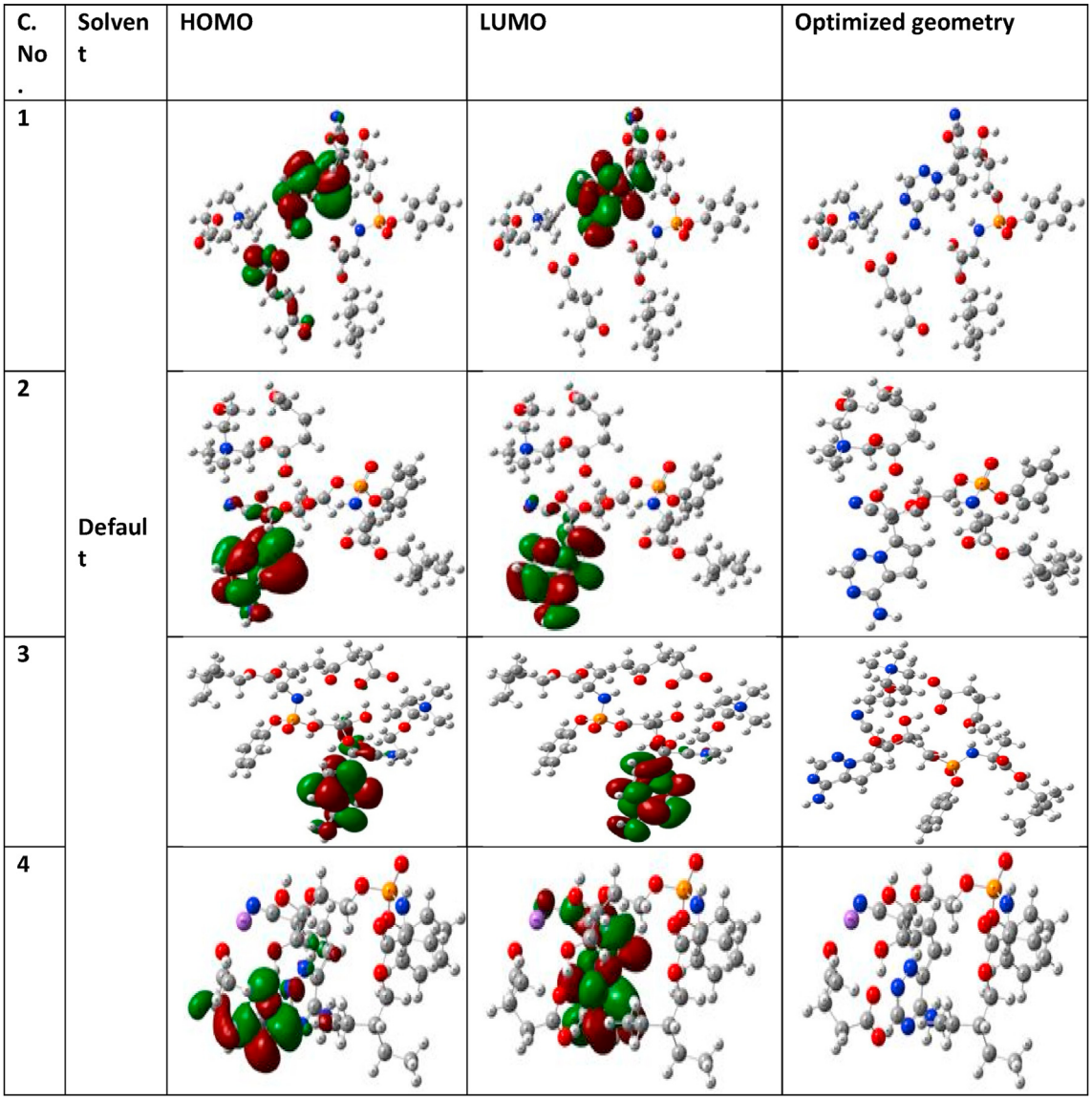


Fig. 1. Frontier orbitals and optimized geometry of (1–5).

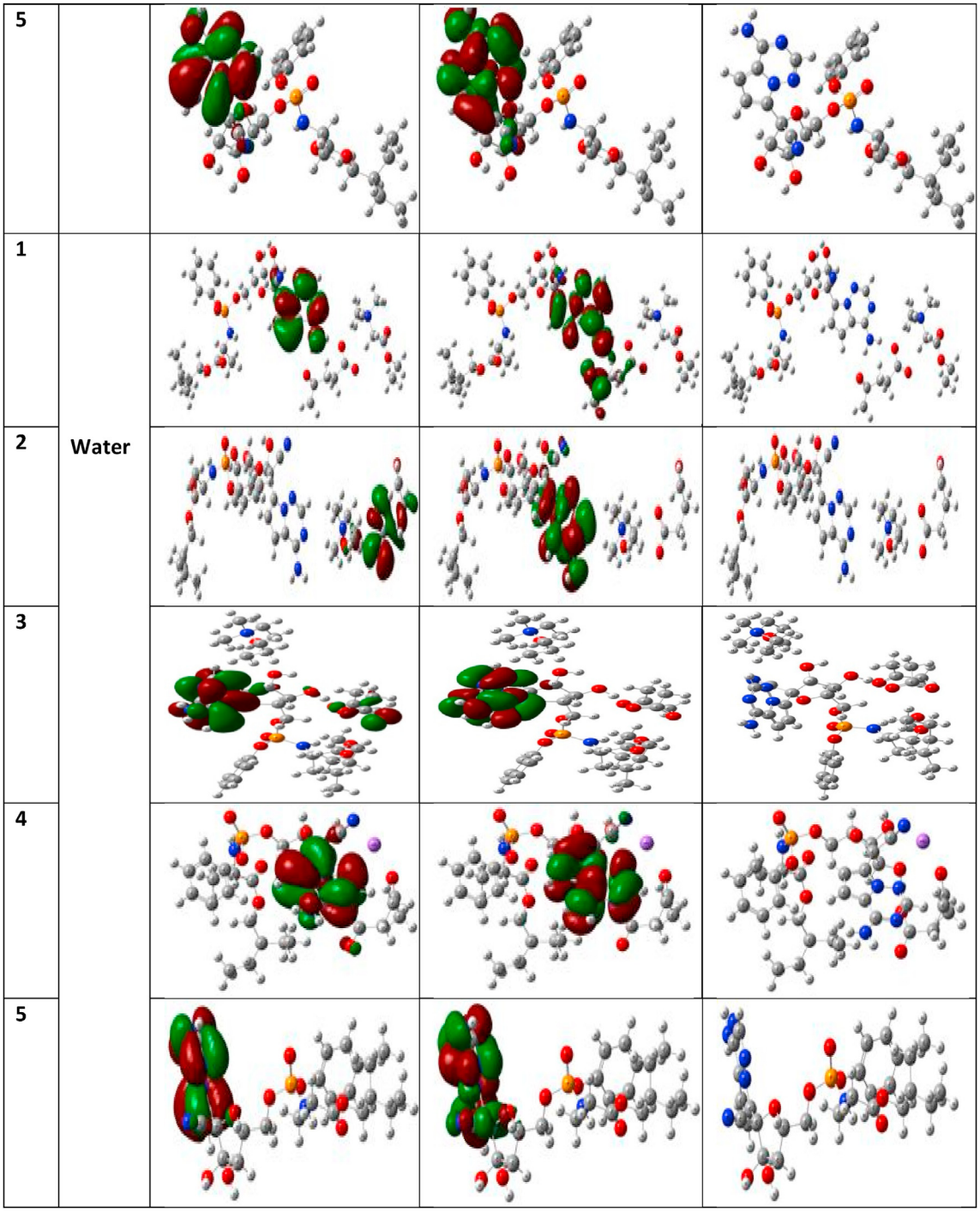


Fig. 1. (*continued*).

Further, the energies of frontier molecular orbitals (HOMO and LUMO) were determined as in Table 3. Further, several physiochemical descriptors like E_{HOMO} - E_{LUMO}, E_{HOMO} + E_{LUMO}, chemical hardness (η), electronegativity (χ), softness (S), chemical potential (μ) and global electrophilicity index (ω) based on energy of HOMO and LUMO using the given equations (1)–(4) below.

$$\mu = (E_{HOMO} + E_{LUMO})\ /2 \text{ equation} \quad (1)$$

$$\chi = -\ (E_{HOMO} + E_{LUMO})\ /2 \text{ equation} \quad (2)$$

$$\eta = (E_{LUMO} - E_{HOMO})\ /2 \text{ equation} \quad (3)$$

$$\omega = \mu 2/\ 2\eta \text{ equation} \quad (4)$$

2.4. DFT-infrared spectra of 1–5 in gaseous and water

Simulated infrared spectra of 1–5 in gaseous and water are plotted to understand different types of stretching as in Fig. 2.

Table 2
Various thermodynamics parameters (zero point energy, thermal energy, thermal enthalpy and thermal free energy) along with optimization energy and dipole moment of 1–5 in gaseous state and in water.

System	Solvent	Sum of electronic and zero-point Energies (a.u.)	Sum of electronic and thermal Energies (a.u.)	Sum of electronic and thermal Enthalpies (a.u.)	Sum of electronic and thermal Free Energies (a.u.)	Optimization energy (a.u.)	Dipole moment (a.u.)
1	Default	−3223.4609	−3223.3944	−3223.3935	−3223.5758	−3224.43126	5.7
2		−3070.8254	−3070.763	3070.762	−3070.9347	−3071.7596	3.1
3		−3149.4039	−3149.3383	−3149.3373	−3149.5190	−3150.3934	4.7
4		−2904.3845	−2904.3306	−2904.3297	−2904.4803	−2905.1187	2.4
5		−2321.5582	−2321.5155	−2321.5145	−2321.6424	−2322.1758	6.5
1	Water	−3223.5319	−3223.4651	−3223.4641	−3223.6533	−3224.5009	19.6
2		−3070.8478	−3070.7831	−3070.7822	−3070.9651	−3071.7774	27.2
3		−3149.4458	−3149.3794	−3149.3784	−3149.5602	−3150.4325	33.6
4		−2904.4541	−2904.3993	−2904.3984	−2904.5522	−2905.1876	5.3
5		−2321.6006	−2321.5574	−2321.5565	−2321.6865	−2322.2127	12.8

Table 3
Various physiochemical descriptors like E_{HOMO} - E_{LUMO}, E_{HOMO} + E_{LUMO}, chemical hardness (η), electronegativity (χ), softness (S), chemical potential (μ) and global electrophilicity index (ω) based on energies of HOMO and LUMO.

C.No.	Solvent	E_L (a.u.)	E_H (a.u.)	$E_{H\text{-}L}$ (a.u.)	E_{L+H} (a.u.)	η (a.u.)	X (a.u.)	S (a.u.)	μ (a.u.)	Ω (a.u.)
1	Default	−0.0366	−0.2178	−0.1812	−0.2544	−0.0906	0.12721	−5.5185	−0.1272	−0.0893
2		−0.0417	−0.2214	−0.1798	−0.2632	−0.0899	0.13158	−5.5614	−0.1316	−0.0963
3		−0.0345	−0.2137	−0.1792	−0.2482	−0.0896	0.1241	−5.5804	−0.1241	−0.0859
4		−0.0396	−0.2106	−0.171	−0.2502	−0.0855	0.12513	−5.848	−0.1251	−0.0916
5		−0.0443	−0.2254	−0.1812	−0.2698	−0.0906	0.13491	−5.5203	−0.1349	−0.1005
1	Water	−0.0404	−0.2229	−0.1825	−0.2632	−0.0913	0.13161	−5.4789	−0.1316	−0.095
2		−0.0492	−0.2194	−0.1701	−0.2686	−0.0851	0.13432	−5.8782	−0.1343	−0.1061
3		−0.0466	−0.2291	−0.1825	−0.2757	−0.0913	0.13785	−5.4795	−0.1379	−0.1041
4		−0.0441	−0.2258	−0.1818	−0.2699	−0.0909	0.13495	−5.5015	−0.135	−0.1002
5		−0.0476	−0.2297	−0.1821	−0.2773	−0.0911	0.13866	−5.4912	−0.1387	−0.1056

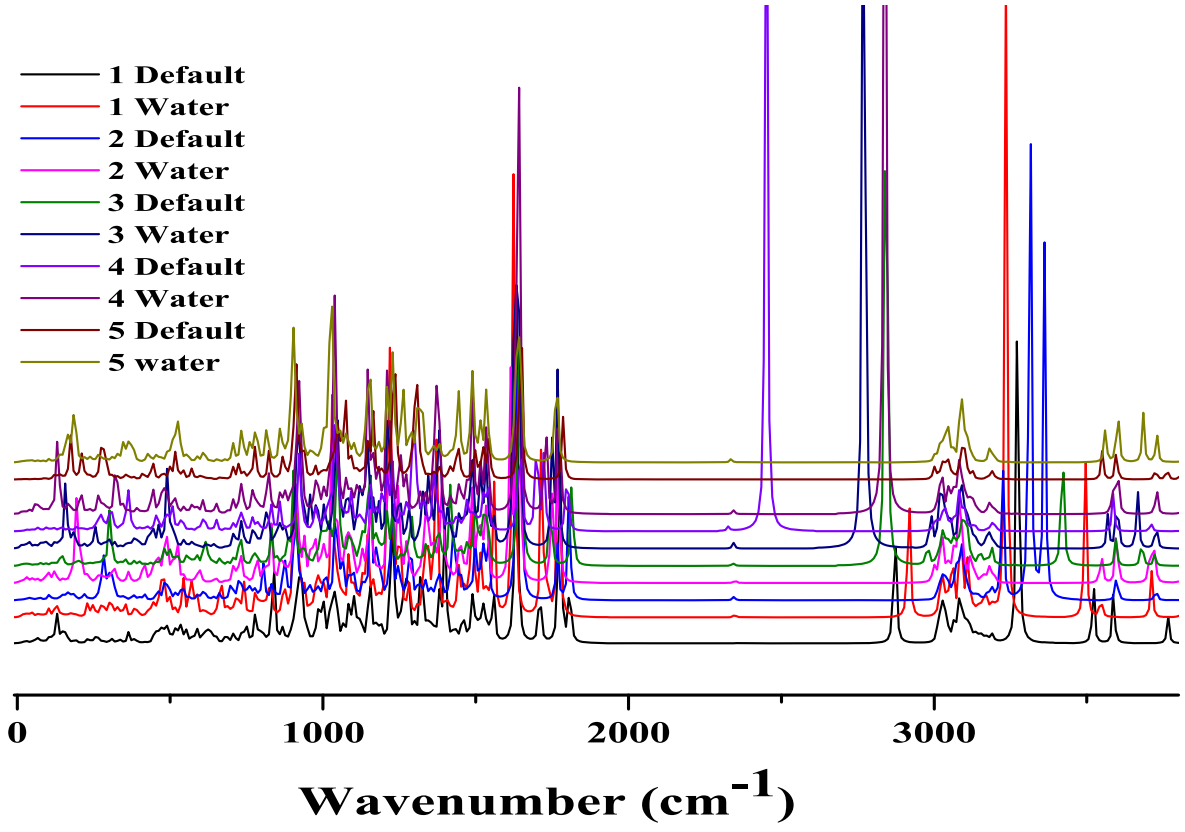


Fig. 2. DFT-IR spectra of 1–5 in gaseous state and water.

Table 4
Binding energies of 1–5 against the Mpro of nCoV.

System No.	System	$E_{binding\ energy}$ (kcal/mol)	E_{VDW} (kcal/mol)	E_{HBond} (kcal/mol)	E_{Elec} (kcal/mol)
1	Remdesivir [Bet-ester] [Lev]	−123.861	−89.6738	−34.1874	0
2	Remdesivir [Chol][Lev]	−129.964	−106.788	−23.1751	0
3	Remdesivir [Chol-ether] [Lev]	−125.446	−93.2485	−33.7789	1.58101
4	Remdesivir Na	−110.358	−90.5188	−19.8394	0
5	Remdesivir	−120.037	−94.3347	−25.7024	0

2.5. Molecular docking

Molecular docking is an important approach to study the interaction of small molecules with the different receptors of interest using computational tools like iGemdock, Pardock [42]. The interaction is studied in teh form of physical data, that is, binding energy due to various interactions like hydrophobic, hydrogen bonding etc [43–45]. Remdesivir (5) with and without ionic liquids (1–4) were docked against Mpro of nCoV. In this work, PDB-6LU7 for main protease of SARS-CoV-2 has been downloaded from RCSB data bank and was prepared using the chimera before docking as in our previous work [16,17]. Then, 1–5 were docked against the main protease of SARS-CoV-2 using the iGemdock, a computational tool as in Table 4.

Synergistic action of remdesivir with the [Chol][Lev], that is, 2 with the amino-acids of main protease of SARS-CoV-2 has been studied based on the binding energy in Fig. 3.

3. Result and discussion

3.1. DFT calculations of the 1–5 in gaseous state and water

Remdesivir (5) with and without ionic liquids (1–4) in gaseous state and water were studied using DFT calculations. Initially, the frontiers molecular orbitals of 1–5 were determined and investigate how the presence of ILs (1–4) affect the orientation of the remdesivir (5). The results have revealed the interactions of ILs (1–4) with the remdesivir and some change in the location of electron density is observed.

Further, the interaction of compound 5 with 1–4 in gaseous state and in water has been studied with the help of the thermodynamic parameters like (zero-point energy, thermal energy, thermal enthalpy and thermal free energy) along with optimization energy and dipole moment. The data presented in Table 2 revealed that thermodynamic energies mainly free energy, a decrease in energy is observed on interaction with ILs (1–4). Authors have taken four ILs having different cations: organic as well as inorganic species. The little variation in thermodynamic energies is observed in water as a solvent. The values of free energies for the 5 (remdesivir) are −2322.1358 and −2322.2127 hartree per particle (a.u.) in gaseous and water respectively but for (1) gaseous and water state are −3223.5758 and −3223.6533 hartree per particle (a.u.) respectively. From this data, it can easily understand that the stability of remdesivir increases in presence of the ionic liquid. The dipole moment of 5 is maximum in gaseous state while the diploe moment of 3 is maximum in water. One should understand the solubility or the dipole moment obtained via DFT calculations on taking water as the physiological system in human in aqueous. Therefore, 3 has promising solubility in water based on the dipole moment. This information is really exciting and will surely investigate this in future assignment.

3.2. Physiochemical descriptors using DFT calculations

The energies of HOMO and LUMO were calculated and based on them, various physiochemical descriptors like E_{HOMO} - E_{LUMO}, E_{HOMO} + E_{LUMO}, chemical hardness (η), electronegativity (χ), softness (S), chemical potential (μ) and global electrophilicity index (ω) respectively have been determined. The value of E_{HOMO} - E_{LUMO} indicates the stability of 1–5 in gaseous and water, 5 has least energy of HOMO in gaseous state while 3 have least energy of HOMO in water, therefore, may react with electrophiles easily in respective medium. All the structures are stable as the value of chemical potential is negative. The value of chemical softness and hardness support the hypothesis. Dipole moment indicates the ability for charge transfer as well as polarity, 3 has highest dipole moment in water based on DFT calculations.

3.3. Simulated DFT-IR spectra of remdisivir (5) with and without ionic liquids (1–4) in gaseous state and water

The intensities bands occurring in the vibrational spectra of 1–5 in water studied. The normal vibrations calculated at the DFT level in the range of 4000–0 cm^{-1} as in Fig. 1.

3.3.1. -OH stretching of alcohol (4000-3500 cm^{-1})

For **1 in gaseous state**, three small peaks are obtained at 3950, 3690 and 3520 cm^{-1} respectively while **in Water**, peaks are observed at 3810 and 3500 cm^{-1}. For **2 in gaseous state**, small peaks are appeared at 3910 and 3700 cm^{-1} while in **water**, intense and small peak observed around

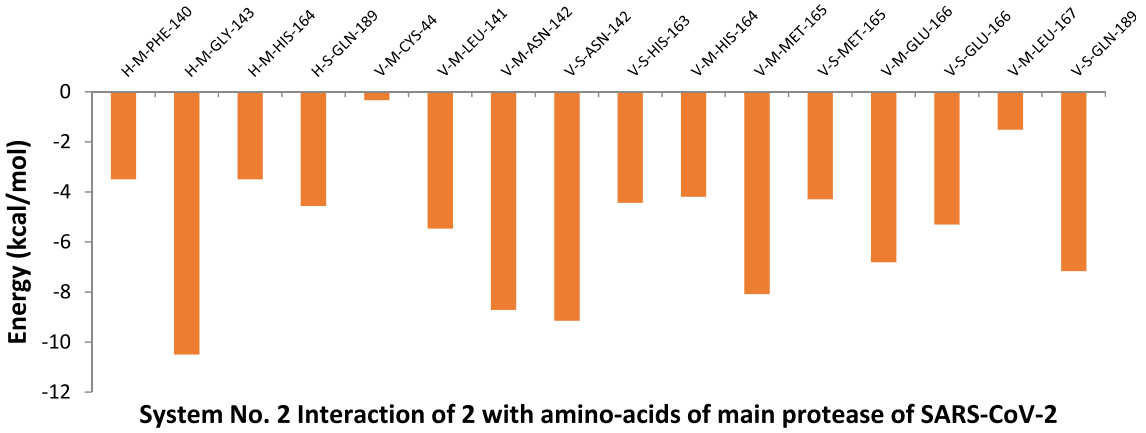


Fig. 3. Synergistic action of remdesivir with the [Chol][Lev], (2) with the amino-acids of protease of SARS-CoV-2.

3910 cm^{-1}. For **3 in gaseous state**, stretching are found at 3820 at 3650 cm^{-1} while in **water**, three peaks are present at 3810, 3680 and 3610 cm^{-1}. For **4 in gaseous state**, a single peak is observed at 3630 cm^{-1} while in **water**, two stretching are observed at 3810 and 3660 cm^{-1}. For **5 in gaseous state**, two peaks are observed at 3650 and 3590 cm^{-1} while in **water**, four peaks are observed at 3810, 3780, 3610 and 3590 cm^{-1}.

3.3.2. -CH stretching of aldehyde (2500-3000 cm^{-1})

For **1 in gaseous state**, single peak appeared at 2900 cm^{-1} while in **water**, peak is shifted at 2950 cm^{-1}. For **2 in gaseous state**, no stretching is seen while in **water**, an intense peak is observed at 2890 cm^{-1}. For **3 in gaseous state**, an intense peak is observed at 2840 cm^{-1} while in w**ater**, stretching is shifted to 2800 cm^{-1}. For **4 in gaseous state**, peak is observed at 2500 cm^{-1} while in **water**, peak is shifted to 2910 cm^{-1}.

3.3.3. C=O stretching (1500-2000 cm^{-1})

For **1**–**5** in **gaseous state** and **water**, a strong and intense peak is observed in the range of 1650–1710 cm^{-1}.

3.3.4. P=O stretching and C–H bending of methylene and methyl group (1000-1500 cm^{-1})

For 1–5 **(gaseous and water),** peaks for C–H bending were observed in the range of 1300–1500 cm^{-1}; a strong and one weak peak of P═O stretching also recorded in 1130–1295 cm^{-1}.

3.3.5. -C═C- bending of mono substituted and di-substituted alkene (500-1000 cm^{-1})

Various peaks of –C═C- bending for 1–5 in **gaseous state** and **water** are appeared in the range of 500–1000 cm^{-1}.

3.4. Molecular docking

The molecular docking of 1–5 against the main protease of SARS-CoV-2 has been performed using iGemdock. Based on the results obtained, it is clear that remdesivir-[Chol][Lev], 2 binds effectively with the main protease of new coronavirus and the obtained for the formation of complex binding energy is −129.964 kcal/mol while the binding energy for remdesivir alone is −120.037 kcal/mol. It means remdesivir in presence of the IL interacts effectively with the main protease of new coronavirus. But an interesting observation is found that when the cation of IL is inorganic, that is, sodium, the binding is less effective than with the remdesivir alone. Remdesivir [Chol][Lev], 2 showed effective binding with the GLY, ASN, MET and GLN of the main protease of new coronavirus. Further, remdesivir [Chol-ether][Lev], 3 also showed promising effective binding against Mpro of nCoV after 2.

4. Conclusion

In the present work, authors have thoroughly studied the interaction of remdesivir with ILs having different cations using density functional theory calculation. Based on the DFT calculations, it is found that remdesivir get more stability on interaction with ionic liquids. Remdesivir-[Bet-ester][Lev] (1) was found to be most stable with free energy of −3223.5758 and −3223.6533 hartree per particle in default and water respectively. 2 and 3 have a comparative stability. Further, the remdesivir was docked with and without ionic liquids having different cations against the main protease of SARS-CoV-2. Results revealed that Remdesivir-[Chol][Lev], **2** have shown the best results against the main protease of SARS-CoV-2 and the binding energy is −129.64 kcal/mol and remdesivir-[Chol-ether][Lev], **3** showed the promising potential with binding energy of −125.446 kcal/mol while Remdesivir [Bet-ester][Lev], **1** gave binding energy of -123.861 kcal/mol. On using sodium as cation in ionic liquid, the obtained binding energy is less than for remdesivir alone. It indicated that the binding energy for the formation of complex is better in presence of ionic liquids having organic cation.

Availability of data and material: (data transparency)

The data is available and will be made available to the journal or any reader on reasonable request.

Code availability

N/A.

Declaration of competing interest

"I, Prashant Singh (Corresponding Author), declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. I further confirm that the order of authors listed in the manuscript has been approved by all of us. There is also no potential conflict of interest.

Acknowledgement

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