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Cuspareine as alkaloid against COVID-19 designed with ionic liquids: DFT and docking molecular approaches

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A B S T R A C T
Cuspareine as a antiviral alkaloid can be used in the treatment of COVID-19. In this study, we introduced the ionic liquids (ILs) concluded cuspareinium as a cation with CH₃COO⁻, CF₃COO⁻, and PF₆ as anions. The optimized geometry, thermodynamic parameters, and reactivity descriptors were calculated with density functional theory (DFT) approach and time-dependent density functional theory (TD-DFT) using B3LYP/6-311G. In addition, the UV and IR spectra of the introduced ILs were investigated. Based on DFT calculation, the designed IL CH₃COO⁻ can be to the most suitable anions due to most solubility in the water. DFT studies displayed that all the introduced ILs have more polarity than pristine cuspareine and CH₃COO⁻ cuspareine is the most polarity due to high dipole moment. Also, the thermo-chemical data of the designed ionic liquids revealed that PF₆-cuspareine is distinguished to be stable. A molecular docking study of the designed ILs with 6 LU7 protease was performed to display interactions and binding energy. Results of molecular docking displayed that CH₃COO⁻ ion liquid has the highest binding energy (~ 7.20 kcal/mol) and Ala7, and Lys 5 residues are involved in an interaction. DFT and molecular docking studies of cuspareine as alkaloid based on ionic liquids can be helpful to for more pharmaceutical and biological researches of cuspareine as an antiviral agent against COVID-19.

1. Introduction

A novel coronavirus, introduced as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the aetiological agent responsible for the 2019–2020 viral pneumonia prevalence of coronavirus disease 2019 (COVID-19) [1-Ali]. Until now, anti-viral medicines like remdesivir, oseltamivir, ganciclovir, ribavirin, favipiravir, nelfinavir, arbidol, remdesivir and galidesivir are being tested for COVID-19 treatment [2–6]. Also, it has been reported that a combination of antiviral drugs with hydroxychloroquine and azithromycin may be the best option to treatment of the patients, based on the patient’s conditions and symptoms [1]. Wang et al. (2020) offered that a combination of remdesivir and chloroquine can be useful for COVID-19 treatment [7]. However, approved vaccines have been applied for the prevention of COVID-19, but still is needed for designing and synthesis of more safer and more effective medicines mainly from plant resources. Quinoline and quinazoline alkaloids are N-based heterocyclic compounds with a wide range of activities, and many of them have been reported to have antiviral effects [8,9]. Therefore, vitally important to assay their efficiency in COVID-19.

The alkaloid of cuspareine is a natural tetrahydroquinoline compound. The extract containing this alkaloid as cytotoxic and antimalarial substances has been used to treat dysentery, fever, and other pains [10,11]. The cuspareine has been exhibited antimalarial activity against resistant strains of malaria, and it has moderately solubility [12]. Also, cuspareine as a quinazoline alkaloid can show antiviral effects. Therefore, it can be used to treat COVID-19, and its effectiveness to be investigated [13]. However it has poor solubility. One of the reasons for the unacceptable variation in pharmacokinetic of some the compounds is their poor solubility [14-16].

The ionic liquids (ILs) are the organic compound with ions impotent coordinated, which are in liquid form at low temperature and have very little dew pressure [17]. These are prepared by ions and small life ions. These are entitled as melts, electrolytes, fused salts, ionic glasses, designer solvents, green solvents and ionic fluid. The ionic liquids illustrate non-flammability, compound and thermal stability, elevated ionic conductivity, non-flammability, and a broad electro-chemical latent pane. Also ionic liquids are available as sealants, electrolytes, and electric battery fluids [18]. Due to unique solvent properties of ILs, they are used in high performance liquid chromatography (HPLC),
capillary electrophoresis, electrochemistry, and spectroscopy [19].

Synthesizing salts by chemical reactions, is a convenient and straightforward method to increasing of solubility that they are recognized as ionic liquids (ILs) [20–22]. The ionic liquids may be hydrophobic and hydrophilic as per the structure of cations, anions, and an alkyl chain on cations/ anions, which makes them polar. These eco-friendly solvents can replace organic solvents in synthesizing polymers, catalytic reactions, biopreservation processes, and enzyme extraction. Also, they can be used as corrosion inhibitors and stabilizers [23–25].

Almost, the most of usable medicines are ionic liquids because, the association of a pharmaceutically active cation and pharmaceutically dynamic anion leads to the formation of active and effective ionic liquid [30].

Recently, ILs are widely used in the field of in pharmacuetics and medicine sciences for increasing solubility and bioavailability of drugs [27–31]. Male and coworkers showed that activity and enzyme stability remain high in methylimidazolium-based tetrafluoroborate [32]. Also, investigations have been confirmed that the stability of serum albumin and myoglobin is increasing in the presence of aqueous IL solutions [33,34]. Molecular docking of imidazolium-based HSO₄–CH₃COO– and NO₃–ILs with cysteine proteinase enzyme-stem bromelain (BNN) have been reported [35]. DNA binding and molecular docking studies have been performed on new imidazolium- based phenylacetamide ionic liquid by Rezky and coworkers [36]. Investigation of nocaspine anticancer drug designed with ionic liquids to enhance solubility with DFT approach by Kumar et al. [37]. The structural, electronic, topological, reactivity, and vibrational properties of Niclosamide as an antiviral agent for treatment of COVID-19 based on B3LYP/6-31G* calculations and molecular docking are investigated by Romani and coworkers [38].

Also, compounds of L-pyroglutamic acid, succinic acid, L-pyroglutamic acid, 2- amino-5-chloropyridine hydrogen succinate, N-phenyl-thioacetamide, selenomethionine and, epigallocatechin Gallate as potential candidate antiviral drugs for the treatment of the COVID-19 with DFT calculations in level B3LYP/6-311++G**) and molecular docking have been studied [39]. Antiviral activities of hydroxychloroquine and hydroxychloroquine sulfate molecules against COVID-19 diseases have been investigated by DFT and molecular docking methods [40].

In the present work, we offered cusparein based ionic liquids using the density functional theory approach to realize their reactivity descriptors and thermodynamics parameters. Further, we attempted to investigate the interaction among the ions of ILs and various amino acids present in protease 6LU7 using a molecular docking approach. Also, a molecular docking study of the cusparein based ionic liquid was carried out to clarify the probable binding modes between the title compound and protease 6LU7 that is a potential target for the inhibition of coronavirus replication [41].

2. Methods

2.1. DFT Approach

Three ionic liquids were introduced using cuspareine as a cation with different anions as CH₃COO–, CF₃COO–, and PF₆. The most stable molecular structures of the cuspareine based ionic liquids were optimized with the Gaussian 9.0 software suite [42] by based density functional theory (DFT) approach [43,44] using the B3LYP function with the 6-311G basis set. The use of 6-31G in density functional theory calculations has been observed in investigation of some antiviral N-Heterocyclic [45] and some glucocorticoids [46] as COVID-19 drugs. All optimizations and frequency calculations in water solvent were performed with the SCRF method of the polarizable continuum model (PCM). Different physico-chemical descriptors of cuspareine based ionic liquids are computed from the energies of HOMO and LUMO frontier molecular orbital. Also, some the thermodynamic parameters are determined for predicting the most stable cuspareine based ionic liquid.

Further, spectroscopic investigation and time dependent-DFT is performed for the Cuspareine and the designed ILs based on Cuspareine based on several papers [47–50].

2.2. Molecular Docking

Molecular docking is one of the computational methods which investigates non-covalent interactions between ligand and protein. The affinity and strength ligand for interaction with protein is displayed by binding energy. We used Viewer lite to prepare the docking suitable structure formats of the cuspareine based ionic liquids, and protease 6LU7. To adding Gasteiger partial charges and polar hydrogens, files of protein and ligands were converted PDBQT format in MGLTOOLS. Then, molecular docking was accomplished using the Lamarckian genetic algorithm [51]. To identify the binding sites in 6LU7 protease. Blind docking has been performed by the grid size set to 80, 80, and 80 Å along with X-, Y- and Z-axes with 9.526, 22.699, and −23.362 Å grid space using Auto Dock 4.2 [52]. The conformation with the lowest binding free energy and low inhibition constants was employed for better analysis. The software package Accelrys Discovery and Ligplos was used to demonstrating and to study the cuspareine based ionic liquids, and protease 6LU7 interactions.

3. Results and Discussion

3.1. Physico-Chemical Properties

Cuspareine as cation with different anions as CH₃COO–, CF₃COO–, and PF₆ are designed. The reactivity descriptors as the softness, hardness, electronegativity, electrophilicity, and gap energy of studied compounds are determined from the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). HOMO, LUMO, and optimized geometry of all of the systems are illustrated in Fig. 1.

The reactivity descriptors are listed in Table 1. The electron-donating ability and the electron acceptance ability of ion liquid systems are distinguished by HOMO and LUMO, respectively. More the value of $E_{\text{HOMO}}$ of the designed IL has CH₃COO– displays more the ability of electron donation. The energy gap values were computed for these compounds, which indicated the stability, and bioactivity of the molecules. More the value of the energy gap expressed more the reactivity of the molecule. The reactivity of the designed IL CH₃COO– anion is the maximum value (−5.0939 eV). The chemical hardness ($\eta$) indicates the stability of the systems.

Several thermodynamic functions of the cuspareine, and the ILs (CH₃COO–, CF₃COO–, and PF₆) were determined using the DFT method. Herein, dipole moment, free energy, optimization energy and enthalphy are obtained for the cuspareine and the ILs (CH₃COO–, CF₃COO–, and PF₆) that are listed in Table 2. The dipole moment of cuspareine, 1 is 6.35 Debye, which indicated this compound has poor polarity and also poor solubility in water. The dipole moment of CH₃COO–, CF₃COO–, and PF₆ is 14.26, 10.34 and 12.50, respectively. These data displayed that all the ion liquids have more dipole moments than cuspareine. Therefore all the considered ILs can have more solubility in water, and CH₃COO anion has the highest polarity.

3.2. Thermodynamic Parameters

Thermodynamics parameters of the free energy, the enthalphy, and the optimized energy of the designed compounds are characterized. The enthalphy of all the designed ILs is lower, more cuspareine that indicates they are more stable than pristine cuspareine and ion liquid having PF₆ has the maximum stability. Calculated free energy of compounds displayed that all ILs causes reduction of free energy and increase of stability. Also, The optimized energy of ion liquid having PF₆ (−1923.5105 Hartree) indicated that it is the most stable.
3.3. IR Spectra

The intensities and wavenumbers of bands for cuspareine and introduced ILs are investigated using frequency of DFT calculations. IR spectra of cuspareine and introduced ILs in the range of 0-3500 cm$^{-1}$ is illustrated in Fig. 2.

**Table 1**
The gap energy, global hardness, and electronegativity (eV) for cuspareine and ILs.

| Compound       | HOMO   | LUMO   | Optimized geometry |
|----------------|--------|--------|--------------------|
| Cusp           | -4.6969| 2.7079 | 2.3485             |
| Cusp-CH$_3$COO | -5.0939| 3.0553 | 2.5469             |
| Cusp-CF$_3$COO | -4.8609| 3.3358 | 2.3404             |
| Cusp-PF$_6$    | -3.4874| 4.0003 | 1.7437             |

**Table 2**
The Optimization energy, the enthalpy, the Gibbs free energies (Hartree) and dipole moment (Debye) for cuspareine and ILs.

| Compound       | Dipole moment | enthalpy | free energy | Optimization energy |
|----------------|---------------|----------|-------------|---------------------|
| Cusp           | 6.3473        | -981.8792| -981.9564   | -982.3153           |
| Cusp-CH$_3$COO | 14.2609       | -1210.9078| -1210.9979 | -1211.4125          |
| Cusp-CF$_3$COO | 10.3382       | -1508.7646| -1508.6686 | -1509.1526          |
| Cusp-PF$_6$    | 12.5010       | -1923.1291| -1923.0327 | -1923.5105          |

**C—H stretching:** In IR spectrum of pristine cuspareine, aromatic C—H stretch appeared in 3067, 3030, 3005 cm$^{-1}$, and methyl C—H stretch in 2950, 2843 cm$^{-1}$, on moving spectra of ionic liquids, the peaks C-H stretching goes to shorten and broad in cuspareine based on CH$_3$COO$^-$ and weak and broad in cuspareine based on CF$_3$COO$^-$. While...
For IR spectrum of pristine cuspareine, the peak of C=C stretching is strong and intense. For IR spectrum of pristine cuspareine, the peak of C=C stretching is strong and intense in the range of 1516-1556 cm⁻¹. In cuspareine based on CH₃COO⁻, the peak of C=C stretching increases to long and sharp. In cuspareine based on CF₃COO⁻, the peak of C=C stretching are more strong and intense and for cuspareine based on PF₆⁻, there is no significant change in the intensity of C=C stretching peaks.

C-O stretching of alkyl aryl ether (1275–1140 cm⁻¹): For IR spectrum of pristine cuspareine, the peak of C=O stretching of alkyl aryl ether shows medium and sharp symmetric and a symmetric stretches but after interaction with ionic liquids the intensity of C-O stretching peaks decreases in the cuspareine based on CH₃COO⁻, cuspareine based on PF₆⁻ while in spectra cuspareine based on CF₃COO⁻, the peak of C=O stretching increases to long and sharp in large extent.

C≡N stretching (1250–1020 cm⁻¹ – 1): For IR spectrum of pristine cuspareine, the peak of C≡N stretching is short and sharpened but after interaction with ionic liquids the peak of C≡N stretching intensity decreased.

C≡C bending (840–790 cm⁻¹ – 1): For IR spectrum of pristine cuspareine, the peak of C≡C bending is very short and difficult to observe but after interaction with ionic liquids the peaks of cuspareine based on CH₃COO⁻, cuspareine based on CF₃COO⁻, increases slightly, while in cuspareine based on PF₆⁻, C≡C bending was also very short.

3.4. TD-DFT Calculation

TD-DFT calculations for the cuspareine, and the introduced ILs (CH₃COO⁻, CF₃COO⁻, and PF₆⁻) were studied at TD-DFT-B3LYP/6-31+G(d,p) level in water solvent. The oscillator strengths and excitation energies for cuspareine, and the introduced ILs (CH₃COO⁻, CF₃COO⁻, and PF₆⁻) are listed in Table 3. The light-harvesting efficiency (LHE = 1 – 10⁻⁵) was approximately calculated from oscillator strength [53].

As can be seen from Table 3, H → L transition dominantly dictate the electronic absorption profile of pristine cuspareine, and cuspareine based on PF₆⁻ with sufficiently high f-values. While strongest absorption of cuspareine based on CH₃COO⁻, and cuspareine based on CF₃COO⁻ with higher LHE values was H → L and H → L + 2 respectively. However, with the interaction of the drug with all three ionic liquids, the probability of transmissions increased and reached to 99.83% for cuspareine based on PF₆⁻.

The oscillator strength is defined as ratio the amount of the quantum
5

that the formation of a 3.23 Å length hydrogen bond between amino acid residue Tr 111, and the hydroxy group of the drug. Also, the formation of a 3.09 Å length hydrogen bond between the hydroxy group of drug, and Gln 110 amino acid is displayed. The value of binding energy of pristine cuspareine with 6 LU7 protease is −6.66 kcal/mol.

The molecular docking of cuspareine having CH$_3$COO$^-$ ion liquid with 6 LU7 protease (Fig. 4(b)) are showed that Ala 7 (bond length, 2.71 Å) and Lys 5 (bond length, 2.36 Å) amino acids play an important role in interactions and has created - 7.20 kcal/mol binding energy. These bonds indicates that the formation of complex ligand (cuspareine having IL) - 6 LU7 protease is stable.

Analysis of molecular docking of cuspareine having CF$_3$COO$^-$ and PF$_6$ ion liquids with 6 LU7 protease are displayed that there is not much change in binding energy (~6.33 and ~6.67 kcal/mol, respectively) compared to pristine cuspareine.

4. Conclusion

Since coronaviruses quickly mutates, designing a novel medicine is very important for control and prevention of COVID-19 pandemic. Molecular docking and density functional theory methods can facilitate on designing and synthesis a biocompatible COVID-19 drug effective and the faster way. Cuspareine is a natural tetrahydroquinoline and demonstrated antiviral effects. It can be used in the treatment of COVID-19. Nevertheless, it has moderate solubility in water. Four ion liquids based on the cuspareine presented for increasing its solubility. DFT studies displayed that all the introduced ILs have more polarity than pristine cuspareine and CH3COO$^-$–cuspareine is the most polarity due to high dipole moment. Also, PF6-cuspareine is distinguished to be stable based on thermodynamic parameters as the free energy, the enthalpy, and optimization energy. As well as, the IR and UV spectrum of the cuspareine and all the introduced ILs on cuspareine were investigated. Also, the interaction between ILs and 6 LU7 protease and the antiviral activity of cuspareine and cuspareine based ionic liquids are evaluated using the molecular docking method. The molecular docking of CH$_3$COO$^-$ ion liquid with 6 LU7 protease illustrated that this ion can bind with 6 LU7 protease and anticipated - 7.20 kcal/mol binding energy. Ala 7 and Lys 5 amino acids of 6 LU7 protease have participated in the interaction. This study can be practical and useable in pharmaceutical applications of cuspareine based ionic liquids as anti viral agents. So, the designed ionic liquids may be used as good antiviral candidates for treating COVID-19. We found that ILs have notable potential against virus protein which create the category to better design ILs with enhancement antiviral activity against virus protein.

Table 3

| Compound | $E_{ex}$ | f | LHE | Transition assignment |
|----------|----------|---|-----|-----------------------|
| Cusp     | Excited  | 0.0020 | 0.0045 | H → L (96.45%) |
| States   | 288.61 nm | 4.361 eV | 0.0066 | 0.0151 | H → L + 1 (88.85%) |
|          | 283.84 nm | 4.4470 eV | 0.0380 | 0.08378 | H → L (79.94%) |
|          | 278.81 nm | 4.1119 eV | 0.0213 | 0.04786 | H → L + 1 (86.39%) |
|          | CH$_3$COO | 301.53 nm | 4.3527 eV | 0.0002 | 0.00046 | H → L + 1 (86.21%) |
|          | Excited  | 284.85 nm | 3.9609 eV | 0.0191 | 0.04303 | H → L (87.49%) |
| States   | 313.02 nm | 4.0918 eV | 0.0009 | 0.00207 | H → L (99.83%) |
|          | CF$_3$COO | 303.01 nm | 4.1816 eV | 0.0001 | 0.00023 | H → L + 1 (99.79%) |
|          | Excited  | 296.50 nm | 4.7251 eV | 0.0100 | 0.02276 | H → L + 2 (96.90%) |
| States   | 262.39 nm | 3.6025 eV | 0.0004 | 0.00092 | H → L (99.83%) |
|          | CF$_3$COO | 344.16 nm | 3.7295 eV | 0.0001 | 0.00023 | H → L + 1 (99.82%) |
|          | Excited  | 322.44 nm | 4.3203 eV | 0.0002 | 0.00046 | H → L + 1 (99.75%) |
| States   | 286.98 nm | 4.4470 eV | 0.0002 | 0.00046 | H → L (99.75%) |

Fig. 4. Molecular docking results of Cuspareine (a) and Cuspareine-CH$_3$COO$^-$ (b) with 6 LU7 protease(c).
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[2] I. Ali, J. Ali, O.M.L. Alharbi, A. Twareq, COVID-19: pathogenesis, clinical features, diagnosis and management, J. Clin. Diagn. Res. 14 (7) (2020) 7–11, https://doi.org/10.7860/JCDR/2020/21002.16218.
[3] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[4] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[5] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[6] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[7] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[8] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[9] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[10] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[11] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[12] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[13] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[14] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[15] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[16] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[17] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[18] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[19] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[20] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[21] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[22] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[23] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
[24] I. Ali, O.M.L. Alharbi, COVID-19: disease, management, treatment, and social impact, Sci. Total Environ. 523–524 (2015) 1053–1067, https://doi.org/10.1016/j.scitotenv.2015.06.107.
J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V.G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hashi, M. Ebara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nokal, T. Vreven, K. Throssell, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M.J. Bearpark, J. Heyd, E.N. Brothers, K.N. Kudin, V.N. Staroverov, T.A. Keith, R. Kobayashi, N. Madadi Mahani et al.

[43] A.D. Becke, Density-functional thermochemistry. III. The role of exact exchange, Chem. Phys. 58 (1993) 5648–5652, https://doi.org/10.1063/1.464913.

[44] C. Lee, W. Yang, R.G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, Phys. Rev. B 37 (1988) 785–791, https://doi.org/10.1103/PhysRevB.37.785.

[45] M. Hagar, H.A. Ahmed, G. Ajlohanai, O.A. Alhaddad. Investigation of some antiviral N-Heterocycles as COVID 19 drug: molecular docking and DFT calculations, Int. J. Mol. Sci. 21 (2020) 3922–3944, https://doi.org/10.3390/ijms21113922.

[46] A.A. Elmaaty, R. Alnajjar, M.I.A. Hamed, M. Khattab, M.M. Khalifa, A.A. Al-Karmalawy. Revisiting activity of some glucocorticoids as a potential inhibitor of SARS-CoV-2 main protease: theoretical study, RSC Adv. 11 (2021) 10027–10043, https://doi.org/10.1039/d0ra10674g.

[47] N. Rekik, N. Issaoui, H. Ghalla, B. Oujia, M.J. Wojcik, IR spectral density of H-bonds. Both intrinsic anharmonicity of the fast mode and the H-bond Bridge. Part I: Anharmonic coupling parameter and temperature effects, J. Mol. Strut. THEOCHEM 821 (2007) 9–21, https://doi.org/10.1016/j.theochem.2007.06.016.

[48] N. Rekik, H. Ghalla, N. Issaoui, B. Oujia, M.J. Wojcik, Infrared spectral density of hydrogen bonds within the strong anharmonic coupling theory: quadratic dependence of the angular frequency and the equilibrium position of the fast mode, J. Mol. Strut. Theocm 821 (2007) 58–70, https://doi.org/10.1016/j.theochem.2007.06.025.

[49] H. Ghalla, N. Issaoui, M. Govindarajan, H.T. Flakus, M.H. Jamroz, B. Oujia, Spectroscopic and molecular structure investigation of 2-furanacrylic acid monomer and dimer using HF and DFT methods, J. Mol. Strut. Theocm 1059 (2014) 152–163, https://doi.org/10.1016/j.molstruc.2013.11.037.

[50] S. Gatlaoui, N. Issaoui, A. Mezni, F. Bardak, T. Roisnel, A. Atac, H. Marosani, Synthesis, structural and spectroscopic features, and investigation of bioactive nature of a novel organic-inorganic hybrid material 1H-1,2,4-triazole-4-ium trifluoromethanesulfonate, J. Mol. Strut. Theocm 1150 (2017) 242–257, https://doi.org/10.1016/j.molstruc.2017.06.092.

[51] R. Dias, W. Filgueira de Azevedo Jr., Molecular docking algorithms, Curr. Drug Targets 9 (2008) 1040–1047, https://doi.org/10.2174/138945008786949432.

[52] G. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility, J. Comput. Chem. 30 (2009) 2785–2792, https://doi.org/10.1002/jcc.21256.

[53] A. Veved, G.W. Ejuh, N. Djionguyang, Study of the optoelectronic and piezoelectric properties of ZrO2 doped PVDF from quantum chemistry calculations, Chin. J. Phys. 63 (2020) 213–219, https://doi.org/10.1016/j.cjph.2019.10.022.