Structural and Spectral characterization, Topological study and activity prediction of antiviral (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol against SARS-CoV-2 Main Protease

asli esme (✉ asliesme@gmail.com)

Kocaeli Universitesi

Research Article

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Abstract

The (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol was deliberated by Ultraviolet-Visible (UV-Vis) and Fourier Transform Infrared (FT-IR) spectroscopy techniques. Hirshfeld surface analysis was performed to analyze the contribution of intermolecular contacts in crystal structure of the studied Schiff base ligand. The plots of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and the electrostatic potential (ESP) were used to research the nucleophilic and electrophilic attack sites for the Schiff base ligand. According to the ESP analysis, the electrophilic reactivity was mainly found in nitro and hydroxy groups attached to phenyl rings, while the nucleophilic attack was more concentrated on hydrogen atoms. Major contributions from molecular orbitals to the electronic transitions computed according to the time-dependent DFT (TD-DFT) method were investigated using chloroform as a solvent. The topological parameters; electron density, Laplacian of electron density, kinetic energy, electron potential energy density, total electron energy density, ellipticity, hydrogen bond energy at the bond critical points have been evaluated. The compound was docked into the severe acute respiratory syndrome coronavirus 2, including a 3-chymotrypsin-like protease receptor's active site with the PDB ID 6LU7. The Schiff base ligand exhibited a good activity against coronavirus main protease receptor with 6LU7 protein as compared with Chloroquine, Favipiravir, and Remdesivir with -4.68 kcal/mol value of the binding energy.

Introduction

Schiff bases, an organic system characterized by an azomethine or imine functional (HC=N-) group, can contain reversible intramolecular proton transfer from an oxygen atom to a neighboring nitrogen atom. Schiff bases can be found in two tautomeric structures as enol ($\text{O-H}\cdots\text{N}$) and keto ($\text{N-H}\cdots\text{O}$) forms^[1]. A Schiff base has reported possessing good electronic and non-linear optical properties ensue from delocalized π - and non-bonding electrons that move along molecule^[2, 3]. If the donor and acceptor groups are increases, non-linear optical properties (the polarizability and first-order hyperpolarizability) of a molecule increase^[4]. The tautomeric forms of the Schiff base can be used as the anion sensors and design of different molecular electronic devices such as optical switches and optical memory devices^[5]. The presence of the azomethine group in heterocyclic Schiff base derivatives has been shown to be critical for various biological activities such as antifungal^[6, 7], antibacterial^[8, 9], antiproliferative^[10], anticoagulant^[11], anti-inflammatory^[12], and antiviral^[13] agents.

The (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol (DNP) compound $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2$ is synthesized and confirmed by single crystal X-ray diffraction studies^[14]. To the best of our knowledge in literature, density functional theory (DFT) calculation of the title compound has not been reported. The investigated compound was examined its structure by infrared spectra (FT-IR) and ultraviolet-visible spectra (UV-Vis). The studies on DNP compound have been carried out DFT based computational study as the topological analysis of Atoms in Molecules (AIM) theory, nonlinear optical (NLO) properties, electronic absorption, vibrational spectroscopic properties, and electrostatic potential (ESP) analysis on molecular van der Waals (vdW) surface used to find the most reactive sites for the electrophilic and nucleophilic attack to support and confirm experimental records^[14]. The calculations of UV-Vis. spectroscopic parameters (oscillator strengths, wavelengths, and excitation energies) of DNP were performed by the time-dependent density functional theory (TD-DFT) method, and the electronic transitions were established in chloroform solvent using GaussSum^[15]. Finally, the study was complemented by molecular docking calculations of DNP compound against SARS-CoV-2 protein, including a 3-chymotrypsin-like protease (PDB ID: 6LU7).

Computational Details

Gaussian 09 Rev. A 11.4^[16] with DFT method using the three-parameter hybrid functional of Becke based on the correlation functional of Lee, Yang, and Parr (B3LYP)^[17, 18] at 6-311++G(d,p) basis set and Gauss View Rev. 5.0.9^[19] software programs were utilized to obtain the molecular geometry optimization of (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol (DNP) compound and to visualize the calculation results, respectively. The vibrational frequencies computed at the DFT/B3LYP functional of the molecule were prepared with the assistance of the VEDA4 program^[20] using the PED - Potential Energy Distribution and compared with the experimental values^[14]. Multiwfn software^[21] has been used to perform Atoms In Molecule

(AIM) analysis, the Critical Bond Point (BCP), the reduced density gradient (RDG), electrostatic potential (ESP) on molecular van der Waals (vdW) surface for DNP.

Results And Discussion

Geometric structure

The crystallographic data for the studied crystalline system in a noncentrosymmetric space group ($P2_12_12_1$) and in an orthorhombic crystal system are $a = 6.6367(2)$ Å, $b = 8.1942(2)$ Å, and $c = 30.9362(9)$ Å^[14]. For the geometry optimization of the title compound, the DFT/B3LYP level of theory with 6-311++G(d,p) basis set was used. The selected optimized geometrical parameters of (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol (DNP) molecule are reported in Table 1 and the optimized molecular diagram with the numbering of atoms is presented in Figure 1.

As a result of intramolecular proton transfer, schiff bases can exist in two tautomeric structures as enol and keto forms in the solid state. The N2 - C7 and O1 - C1 bond distances that are descriptive for Schiff bases were 1.284(4) Å / 1.3012 Å and 1.346(3) Å / 1.3417 Å for X-ray^[14] / DFT/B3LYP results, respectively. The bond distance between N2 and C7 is consistent with an N=C double bond, while the O1 - C1 bond distance is consistent with the O - C single band. The double C=N bond and single O - C bond lengths correspond well with those previously reported for the related compounds^[22, 23]. It is concluded on the basis of DFT results that the H1 atom is located on O1 atom, thus the DNP compound exists in enol form.

The torsion angle (C6-C7-N2-C8) observed as $-178.7(3)^\circ$ ^[14] and calculated at 175.94° is consistent with the corresponding distances in the related Schiff bases structures^[24, 25]. The dinitrophenylimino group is almost coplanar with the attached ring with C6-C7-N2-C8 torsion angle of 175.94° for the DFT/B3LYP method.

This intramolecular hydrogen bond O1-H1...N2 with A...D distance of 2.633(3) Å and A...H-D angle of $146.2(5)^\circ$ ^[14] is characterized by distance of 2.6495 Å and angle of 147.22° using B3LYP/6-311++G(d,p) level of theory, being shorter than the sum of the Van der Waals radius of the N and O atoms (3.07 Å)^[26].

Hirshfeld surface analysis

Hirshfeld surface analysis with Hirshfeld surfaces and two-dimensional fingerprint plots generated with *Crystal Explorer version 3.1 software*^[27] is a useful technique for determining intermolecular interactions in crystal structures. The red and blue spots on the normalized contact distance (d_{norm}) surface given in Fig. 2 represent the contacts with distances shorter (in close contact) or longer (distinct contact) than the Van der Waals radii, respectively. The smaller red areas known to be hydrogen-acceptor regions in Fig. 2 is attributed to O...H/H...O contacts, but representing C-H...O (distance of 2.380 Å) hydrogen bonds between the H13 atom of the hydroxyl group and the O1 atom of the phenyl ring. The two-dimensional fingerprint plots providing information on the percentage contributions of the various interatomic contacts are shown in Fig. 3. The most important are H...H interactions, which contribute 35.6% to the total Hirshfeld surface, while the other contributions are from O...H/H...O (35.8%) contacts. As a result, H...H and O...H/H...O contacts accounted for more than 71.4% of the Hirshfeld surface, whereas the H...C/C...H interaction only contributed to 9.1% of the surface.

Vibrational Analysis

The Fourier transform infrared (FT-IR) spectra of the functional groups present in the structure of DNP compound have been studied by workers^[14]. For visual comparison, the observed^[14] FT-IR bands and calculated wavenumbers investigated with VEDA 4 program by considering PEDs of DNP are depicted in Table 2. Unscaled wavenumbers obtained at the DFT/B3LYP/6-311++G(d,p) level of theory were scaled with a factor of 0.958 for wavenumbers greater than 1100 cm^{-1} and 0.983 for wavenumbers less than 1100 cm^{-1} . The experimental and simulated DFT (B3LYP) FT-IR spectrum of the studied compound is given in Figure 4.

Hydroxy (OH) vibrations

Due to the strong intramolecular interactions between hydroxyl group and imine group in the compound, the O-H stretching vibration mode under intramolecular hydrogen bonding is observed at the interval $3100\text{--}3450\text{ cm}^{-1}$ ^[28]. The experimental^[14] FT-IR

spectrum of DNP was presented the O–H stretching peak at 3415 cm^{-1} . In this study, the O-H stretching vibration which broadens owing to the formation of strong intramolecular hydrogen bonding O–H $\cdots$ N in the DNP was computed as 3127 cm^{-1} with a PED contribution of 98%. The theoretically calculated values at 1517 cm^{-1} (27%) and $812, 808\text{ cm}^{-1}$ (40%, 34%) are assigned to OH group in-plane $\sigma(\text{HOC})$ and out-of-plane $\tau(\text{HOCC})$ modes, respectively, in agreement with the literature data^[29, 30].

Methyl (CH_3) and Methylene (CH_2) groups vibrations

The asymmetric stretching vibrations of the aliphatic CH_3 / CH_2 groups are typically observed in the interval $\sim 2980\text{ cm}^{-1}$ / $3000\text{--}2900$, while the symmetric stretching vibrations are observed at the interval of $\sim 2870\text{ cm}^{-1}$ / $2900\text{--}2800\text{ cm}^{-1}$, respectively^[31, 32]. The asymmetric $\nu_{\text{as}}(\text{CH}_3)$ stretching vibrations (mode nos: 8-11) are occur with the rang $2984\text{--}2966\text{ cm}^{-1}$ with PED contribution of 73-85%, the computed symmetric $\nu_{\text{s}}(\text{CH}_3)$ wavenumbers are at 17 and 18 having wavenumbers at 2908 and 2905 cm^{-1} with PED contribution of $\sim 84\%$. The CH_2 vibrational modes separated as asymmetric and symmetric were calculated at $2953, 2944\text{ cm}^{-1}$ (85%, 89% PED) and $2919, 2915\text{ cm}^{-1}$ (90%, 98% PED) for DNP, respectively, and in good agreement with the literature^[33]. The bending vibrations of these CH_2 and CH_3 groups were found to be at $1464, 1448$ and $1442, 1435, 1433, 1427, 1425\text{ cm}^{-1}$ while twisting modes were observed at 1284 (36%), respectively.

Nitro (NO_2) group vibrations

The asymmetric ($\nu_{\text{as}}(\text{NO}_2)$) and symmetric ($\nu_{\text{s}}(\text{NO}_2)$) stretching vibrations of the aromatic nitro (NO_2) compounds^[34, 35] have strong absorptions at $1485\text{--}1570\text{ cm}^{-1}$ and $1320\text{--}1370\text{ cm}^{-1}$, respectively. In our study, the NO_2 asymmetric and asymmetric stretching modes are observed at $1532, 1512\text{ cm}^{-1}$ and $1319, 1303\text{ cm}^{-1}$ ^[14] and these values are calculated at $1524, 1520\text{ cm}^{-1}$ with PED contribution of 49%, 47% and $1317, 1310\text{ cm}^{-1}$ (B3LYP) with PED contributions of 65%, 79%.

Carbon - Nitrogen Vibrations

The most characteristic region of $1500\text{--}1700\text{ cm}^{-1}$ can be used to describe the N=C stretching vibration of the Schiff base derivatives^[28]. The calculated value for $\nu(\text{C}=\text{N})$ is predicted at 1558 cm^{-1} with PED contribution of 30%, while the azomethine N=C stretching vibration is observed a strong band (Fig. 4) at 1585 cm^{-1} in FT-IR spectrum^[14]. The N-C stretching vibrational for all amine compounds^[36] exhibit in the region $1000\text{--}1350\text{ cm}^{-1}$. The observed stretching band at 1338 cm^{-1} can be assigned to N1-C3 stretching mode for DNP^[14] and this band was calculated at 1392 cm^{-1} (12% PED) using DFT/B3LYP6-311++G(d,p) level of theory. The N-C stretching vibration for 2-[(4-propylphenylimino)methyl]-4-nitrophenol molecule has been assigned at 1178 cm^{-1} using the B3LYP/6-31G(d) method by Ađar et. al.^[37]. In this study, the N2-C8 stretching vibration was calculated at $1183, 974\text{ cm}^{-1}$ for B3LYP level of theory with the 15%, 16% contributions of PED.

Carbon-Carbon Vibrations

The aromatic C=C stretching vibration was observed at the 1637 cm^{-1} experimentally^[14], and calculated as 1608 cm^{-1} (47% PED), which agree well with the literature data. The benzene ring and its derivatives were specified in the range of $1650\text{--}1450\text{ cm}^{-1}$ in terms of the C-C stretching modes^[38, 39]. The C-C stretching vibrations computed at the DFT/B3LYP/6-311++G(d,p) level of theory were obtained in the interval 1608 (47%) / 1324 (42%) cm^{-1} (ring A) and 1593 (29%) / 984 (13%) cm^{-1} (ringB). The reason why these frequencies are slightly different between the rings may be that there is a functional group attached to the ring.

Frontier molecular orbitals analysis

The frontier molecular orbitals (FMOs) which have the advantage of analyzing the chemical properties and kinetic stability of the molecule are illustrated in Fig. 5. The lowest unoccupied molecular orbital energy E_{LUMO} measures the electron-accepting character of a compound, while the highest occupied molecular orbital energy E_{HOMO} assesses its electron-donating character. The HOMO orbitals are mainly located on the whole molecule except NO_2 groups attached to the phenyl ring, while LUMO orbitals are localized mainly on phenyl ring carrying both NO_2 groups.

The energy gap ($\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$), Ionization potential ($I = -E_{\text{HOMO}}$), Electron affinity ($A = -E_{\text{LUMO}}$), Chemical hardness ($\eta = (I - A)/2$), Chemical softness ($\sigma = 1/\eta$), chemical potential ($\mu = -(I + A)/2$), electrophilicity index ($\omega = \mu^2/2\eta$) for DNP have been calculated at DFT/B3LYP/6-311++G(d,p) level of theory and tabulated in Table 3. The energy gap of LUMO – HOMO explains the ultimate charge transfer interaction within the molecule DNP was found to be 2.7317 eV. The high value of the chemical hardness (the low value of the softness) related to the energy gap shows the stability of the molecule. The chemical hardness (η) and softness (σ) obtained using the HOMO and LUMO energies were predicted as 1.3659 eV and 0.7321 eV^{-1} , respectively. The calculated values of ΔE and η for DNP are smaller than those of (E)-2-[(2-Chlorophenyl) iminomethyl]-4-trifluoromethoxyphenol ($\Delta E = 4.081 \text{ eV}$ and $\eta = 2.040 \text{ eV}$) as a comparison to the corresponding Schiff base compound in the literature^[40]. The energy gap (ΔE) and the global hardness parameters (η) of DNP show that the studied Schiff base is not chemically hard, implying that it is highly polarizable and chemically reactive. Besides, the lower electrophilicity index value of 0.6830 eV suggests that the title compound has biological activity^[41].

Electrostatic potential analysis

The electrostatic potential (ESP) on molecular van der Waals (vdW) surface is a major parameter for describing regions responsible for hydrogen bonding interactions as well as potential electrophilic and nucleophilic sites in a molecule^[42, 43]. In the 3D ESP plot van der Waals (vdW) surface along with the surface minima and maxima is shown in Fig. 6a, the color scale of the map ranges between -22.00 kcal/mol and +22.00 kcal/mol. it can be seen that the global surface minimum value (-31.66 kcal/mol) was found at the oxygen atom of the NO_2 group, while the global surface maximum (+28.34 kcal/mol) is about the hydrogen atoms of the CH_3 group. Additionally, the negative regions with the blue color indicate sites for electrophilic reactivity are mainly located on the NO_2 and OH groups attached to phenyl rings, whereas the positive region is more concentrated on hydrogen atoms indicating a possible site for nucleophilic attack. The surface area in different ESP ranges is represented in Fig. 6b. The vdW surface area of the NO_2 and OH groups' moiety is $114.30 \text{ \AA}^2$, which occupies 29.7% of the overall surface.

Ultraviolet-Visible Studies

The percentage contributions of molecular orbitals to formation of the bands were obtained by using Gausssum program 3.0.^[15] For enol form of the studied compound, wavelength (λ , nm), oscillator strength (f , a.u), major contributions of calculated transitions are given in Table 4. Inset of Fig. 7 shows the absorption band at 413 nm (in chloroform) is attributed to the $n \rightarrow \pi^*$ electronic transition^[14]. Considering the TD-DFT calculations, it can be said that the theoretical electronic absorption spectrum of the Schiff base DNP ligand at 379.34 nm arises from HOMO $\rightarrow$ LUMO (97%) transitions.

Topology calculations

Atoms in Molecules (AIM) is an effective and widely used tool for determining intramolecular and intermolecular hydrogen bonding^[44]. According to the topological analysis of Atoms in Molecules (AIM) theory, to assign an interaction between two primary atoms, the intramolecular O-H...N links have investigated to analyze characteristics of the Critical Bond Point (BCP). The calculated electron density (ρ_{BCP}), Laplacian of electron density ($\nabla^2 \rho_{\text{BCP}}$), Lagrangian kinetic energy (G_{BCP}), electron potential energy density (V_{BCP}), total electron energy density (H_{BCP}), ellipticity (ϵ_{BCP}), hydrogen bond energy (E_{HB}) at hydrogen bonding BCPs are represented in Table 5. Hydrogen bonds can be classified as follows^[45], weak hydrogen bonds ($E_{\text{HB}} < 12.0 \text{ kcal/mol}$); $\nabla^2(\rho_{\text{BCP}}) > 0$ and $G(\rho_{\text{BCP}}) + V(\rho_{\text{BCP}}) > 0$; medium hydrogen bonds ($12.0 < E_{\text{HB}} < 24.0 \text{ kcal/mol}$); $\nabla^2(\rho_{\text{BCP}}) > 0$ and $G(\rho_{\text{BCP}}) + V(\rho_{\text{BCP}}) < 0$; strong hydrogen bonds ($E_{\text{HB}} > 24.0 \text{ kcal/mol}$); $\nabla^2 \rho(\rho_{\text{BCP}}) < 0$ and $G(\rho_{\text{BCP}}) + V(\rho_{\text{BCP}}) < 0$ where $G(\rho_{\text{BCP}}) + V(\rho_{\text{BCP}})$ is also known as total electronic energy density, $H(\rho_{\text{BCP}})$. It can be seen in Fig. 8 that 63 index corresponds to the bond critical point (BCP) of the intramolecular hydrogen bond O1-H1...N2. The $\rho(r)$ at the 63 BCP moiety for hydrogen bond is close to 0.04 a.u and $\nabla^2 \rho_{\text{BCP}}$ value is in the range of 0.02 - 0.15 a.u, which is the maximum threshold value ensuring the formation of hydrogen bond^[46]. The V_{BCP} at this BCP is found to be -0.041927 a.u, therefore the hydrogen bond energy $E_{\text{HB}} = 0.5V_{\text{BCP}}$ could be evaluated as $E_{\text{HB}} = -13.154907 \text{ kcal/mol}$. The hydrogen bond energy E_{HB} is -13.154907 kcal/mol, $\nabla^2(\rho_{\text{BCP}}) > 0$ and $G(\rho_{\text{BCP}}) + V(\rho_{\text{BCP}}) < 0$ indicating that the hydrogen bond is medium hydrogen bond.

The reduced density gradient (RDG) derived from electron density as a dimensionless quantity was developed by Johnson et al. [47].

$$RDG(r) = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla^2 \rho(r)|}{\rho(r)^{4/3}}$$

where $\rho(r)$ and $\nabla \rho(r)$ is the electron density and the gradient of $\rho(r)$ at the point r , respectively. RDG is a helpful approach to explore non-covalent interactions (NCI) in real space, such as both intra- and intermolecular weak interactions (like hydrogen bonds) and is represented in Fig. 9. The graphical representation of $\rho(r)$ versus $\text{sign}(\lambda_2)\rho$ are used to explain the repulsive ($\text{sign}(\lambda_2)\rho > 0$), attractive ($\text{sign}(\lambda_2)\rho < 0$) and Van der Waals ($\text{sign}(\lambda_2)\rho \approx 0$) interactions. As can be seen in Fig. 9 (2D scatter plot), the hydrogen bonding interactions between the nitrogen and the hydrogen atoms were detected between -0.020 and -0.005 a.u. The 3D RDG isosurface densities of DNP in Fig. 9 show the non-covalent interactions of DNP including hydrogen bonds, van der Waals interactions and steric effects. The elliptical plate between O–H and imine N atoms shows the more blue region, which means the attractive interactions. As a result of this, we can conclude that there is a strong hydrogen bond.

Nonlinear Optical Properties

The Nonlinear Optical (NLO) activity values of dipole moment μ (D), mean polarizability $\langle \alpha \rangle$ (in a.u. and esu), the anisotropic of the polarizability $\langle \Delta \alpha \rangle$ (in a.u.) and the mean first-order hyperpolarizability β (in a.u. and esu) are calculated using the DFT/B3LYP/6-311++G(d,p) level of theory. The components of dipole moment, mean polarizability, the anisotropic of the polarizability, and the mean first-order hyperpolarizability of the title compound can be seen in Table 6. The β for DNP calculated at the DFT/B3LYP/6-311++G(d,p) level of theory is 85.9094×10^{-30} esu that is approximately 110 times greater than the magnitude of urea (for urea β is found to be $0.7803 \cdot 10^{-30}$ esu^[48] obtained at the same method). The large value of β calculated by the DFT/B3LYP method shows that the title compound has useful NLO properties.

Molecular docking analysis

The PDB file of DNP was generated from the optimized molecular structure of the title compound. The three-dimensional (3D) structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, including a 3-chymotrypsin-like protease (3CL^{Pro}) was downloaded from RCSB PDB database (PDB ID: 6LU7) available at <https://www.rcsb.org/structure/6LU7>^[49]. The behavior of the studied compound into the functional sites of receptor 6LU7 protein was conducted by the Autodock 4.2^[50]. Discovery Studio Visualizer from Biovia was used to evaluate the 2D structure and the nature of interactions between ligand and 3CL^{Pro} (6LU7) protein^[51]. These enzymes were prepared for docking using the PyMOL molecular viewer (VMD)^[52].

The docking results including docking binding energies (kcal/mol), inhibition constants (μM), intermolecular energies (kcal/mol), and amino acid residues that have H-bond interactions with the ligand were listed in Table 7. As can be seen Fig. 10, DNP exhibited up to NO₂ and OH conventional hydrogen bond interactions with LYS5 (5.6 Å), ARG4 (2.1 Å), and PHE3 (3.3 Å) active sites, respectively. The following is the increasing order of binding energies DNP (-4.68 kcal/mol) < Chloroquine (-4.62 kcal/mol) < Favipiravir (-3.88 kcal/mol) < Remdesivir (-3.45 kcal/mol). According to studied results, the DNP compound has a better affinity for the COVID 19 main protease receptor compared to Chloroquine, Favipiravir, and Remdesivir.

Conclusion

The (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol (DNP) was characterized by the Ultraviolet-Visible and Fourier Transform Infrared spectral studies. The H...H contacts have a major contribution for the studied ligand of 35.6% to the total Hirshfeld surface. The vibrational assignments calculated at DFT/B3LYP/6-311++G(d,p) level of theory with the help of PED compared with the experimental values. The theoretical TD-DFT calculations of UV-vis spectrum show the absorption band (413 nm) in chloroform solvent corresponding to H→L+2 (97%). NLO parameter confirms the optical activity of the DNP compound with a high value of first-order hyperpolarizability that is approximately 110 times greater than the magnitude of urea. The topological analysis based on the Atoms in Molecules theory suggest that the nature of the hydrogen bonds present in the studied compound

is moderate due to $\nabla^2(r_{\text{BCP}}) > 0$ and $G(r_{\text{BCP}}) + V(r_{\text{BCP}}) < 0$. Finally, the frontier molecular orbital results showed the highly polarizable and chemically reactive. Therefore, this investigated compound shown good interaction with the sites of 3CL^{pro} may be considered as a potent inhibitor for COVID-19.

Declarations

Funding Not applicable

***Availability of data and material** Not applicable

Code availability Gaussian 09 Rev. A 11.4 package program, VEDA4 program, Multiwfn software

Authors' contributions The manuscript was written by a single author, who has given approval to the final version of the manuscript. The author would like to thank Prof. Dr. S Sagdinc for the technical support.

Conflict of interest The author declares that he has no competing interest.

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Tables

Table 1 Experimental and theoretical selected bond lengths, bond angles and dihedral angles with DFT/B3LYP/6-311++G(d,p) level of theory for DNP

Bond Lengths(Å)	Theoretical calculations		Theoretical calculations		X-Ray ^a
	X-Ray ^a		Bond Angles(°)		
O1–C1	1.346(3)	1.3417	C7–N2–C8	118.8(3)	120.99
O2–N3	1.237(4)	1.2241	C3–N1–C14	120.7(3)	121.45
O3–N3	1.229(4)	1.2219	C3–N1–C16	121.3(3)	121.08
O4–N4	1.221(4)	1.2224	C14–N1–C16	116.4(3)	117.44
O5–N4	1.226(5)	1.2228	C6–C7–N2	123.3(3)	123.01
N2–C7	1.284(4)	1.3012	O2–N3–C10	118.5(3)	117.43
N1–C3	1.361(4)	1.3732	O4–N4–C12	118.0(3)	117.41
N1–C14	1.471(4)	1.4662	Dihedral Angles(°)		
N1–C16	1.466(4)	1.4666	C6–C7–N2–C8	-178.7(3)	175.94
N2–C8	1.413(4)	1.3943	N2–C7–C6–C1	-2.3(5)	-1.05
N3–C10	1.468(4)	1.4855	C7–C6–C1–O1	-6.0(5)	0.38
N4–C12	1.472(5)	1.4857	C4–C3–N1–C14	-9.0(4)	-1.39
			C2–C3–N1–C16	8.3(4)	0.89

^a from Ref [14]; Å: angstrom unit; °: degree.

Table 2 Comparison of the observed and calculated vibrational frequencies (cm⁻¹) with the 6-311++G(d,p) basis set

		Expt. ^a	Theoretical				Expt. ^a	Theoretical	
			B3LYP					B3LYP	
ν	Assignments (%PED ^b)		Unscaled	Scaled	ν	Assignments (%PED ^b)		Unscaled	Scaled
1	$\nu(\text{OH})(98)$	3415	3266	3127	49	$\sigma(\text{HCC})_{\text{phA}}(42)$, $\nu(\text{CC})(13)$		1272	1219
2	$\nu_{\text{s}}(\text{CH})_{\text{phB}}(99)$		3250	3114	50	$\nu(\text{OC})(18)$, $\sigma(\text{HCC})_{\text{phB}}(10)$		1260	1207
3	$\nu_{\text{s}}(\text{CH})_{\text{phA}}(90)$		3229	3094	51	$\sigma(\text{HCC})_{\text{phB}}(57)$		1252	1199
4	$\nu_{\text{as}}(\text{CH})_{\text{phA}}(89)$		3228	3092	52	$\nu(\text{CC})_{\text{phA}}(11)$, $\nu(\text{N2C8})(15)$, $\sigma(\text{HCC})_{\text{phB}}(12)$		1235	1183
5	$\nu_{\text{s}}(\text{CH})_{\text{phB}}(99)$		3227	3091	53	$\nu(\text{NC})(29)$		1216	1165
6	$\nu_{\text{s}}(\text{CH})_{\text{phB}}(99)$		3223	3088	54	$\sigma(\text{HCC})_{\text{phA}}(32)$, $\nu(\text{CC})_{\text{phA}}(14)$		1185	1135
7	$\nu_{\text{as}}(\text{CH})_{\text{phA}}(98)$		3161	3028	55	$\sigma(\text{HCC})_{\text{phA}}(11)$		1161	1112
8	$\nu_{\text{as}}(\text{CH}_3)(84)$		3115	2984	56	$\sigma(\text{HCC})_{\text{phB}}(42)$, $\nu(\text{CC})_{\text{phB}}(11)$		1114	1067
9	$\nu_{\text{as}}(\text{CH}_3)(81)$		3111	2980	57	$\nu(\text{NC})(20)$, $\tau(\text{HCCN})(24)$		1112	1065
10	$\nu_{\text{as}}(\text{CH}_3)(73)$		3100	2970	58	$\tau(\text{HCCN})(36)$		1100	1054
11	$\nu_{\text{as}}(\text{CH}_3)(85)$		3096	2966	59	$\sigma(\text{HCC})_{\text{phB}}(49)$		1087	1041
12	$\nu_{\text{as}}(\text{CH}_2)(85)$		3082	2953	60	$\tau(\text{HCCN})(22)$, $\nu(\text{CC})(30)$		1082	1037
13	$\nu_{\text{as}}(\text{CH}_2)(89)$		3073	2944	61	$\nu(\text{CC})(43)$, $\nu(\text{NC})(23)$		1026	1009
14	$\nu_{\text{s}}(\text{CH}_2)(90)$		3047	2919	62	$\sigma(\text{CCC})_{\text{phB}}(49)$, $\tau(\text{HCNC})(13)$		1014	997
15	$\nu_{\text{s}}(\text{CH}_2)(98)$		3043	2915	63	$\tau(\text{HCNC})(52)$, $\nu(\text{CC})_{\text{phB}}(13)$		1001	984
16	$\nu(\text{CH})(99)$		3037	2909	64	$\nu(\text{N2C8})(16)$,		991	974
17	$\nu_{\text{s}}(\text{CH}_3)(83)$		3035	2908	65	$\sigma(\text{CCC})_{\text{phA}}(15)$		974	957
18	$\nu_{\text{s}}(\text{CH}_3)(84)$		3032	2905	66	$\tau(\text{HCCC})_{\text{phA}}(69)$, $\tau(\text{CCCC})_{\text{phA}}(13)$		952	936
19	$\nu(\text{CC})_{\text{phA}}(47)$, $\sigma(\text{HOC})(12)$	1637	1678	1608	67	$\tau(\text{HCCN})_{\text{phB}}(80)$		946	929
20	$\nu(\text{C=N})(13)$, $\nu(\text{CC})_{\text{phB}}(29)$		1663	1593	68	$\nu(\text{NC})(33)$, $\sigma(\text{NO}_2)(25)$		930	914
21	$\nu(\text{C=N})(30)$, $\sigma(\text{HC=N})(13)$	1585	1627	1558	69	$\tau(\text{HCCN})_{\text{phB}}(61)$		926	910

22	$\nu_{\text{as}}(\text{NO}_2)(21),$ $\nu(\text{CC})_{\text{phB}}(26)$		1621	1553	70	$\tau(\text{HCCN})_{\text{phB}}(56)$	921	905
23	$\nu_{\text{as}}(\text{NO}_2)(49)$	1532	1591	1524	71	$\sigma(\text{CCC})_{\text{phA}}(35)$	892	877
24	$\nu_{\text{as}}(\text{NO}_2)(47),$ $\nu(\text{CC})_{\text{phB}}(11)$	1512	1587	1520	72	$\tau(\text{HOCC})(12),$ $\tau(\text{HCCN})_{\text{phA}}(56)$	853	838
25	$\nu(\text{CC})_{\text{phA}}(12),$ $\sigma(\text{HOC})(27)$		1583	1517	73	$\sigma(\text{NO}_2)(32)$	844	830
26	$\sigma(\text{HCC})_{\text{phA}}(22),$ $\nu(\text{CC})_{\text{phA}}(25),$ $\nu(\text{N1C3})(11)$		1547	1482	74	$\tau(\text{HOCC})(40)$	826	812
27	$\sigma(\text{CH}_2)(58)$		1528	1464	75	$\tau(\text{HOCC})(34)$	822	808
28	$\sigma(\text{CH}_2)(64)$		1512	1448	76	$\tau(\text{HCCC})_{\text{phA}}(61)$	796	782
29	$\sigma(\text{CH}_3)(51)$		1505	1442	77	$\gamma(\text{HCNC})(28),$ $\gamma(\text{HCCN})(21)$	791	778
30	$\sigma(\text{CH}_3)(56)$		1498	1435	78	$\gamma(\text{HCNC})(15),$ $\gamma(\text{HCCN})(19)$	787	774
31	$\sigma(\text{CH}_3)(55)$		1496	1433	79	$\sigma(\text{NO}_2)(31),$ $\sigma(\text{CCC})_{\text{phB}}(25)$	748	735
32	$\sigma(\text{CH}_3)(42)$		1490	1427	80	$\gamma(\text{NO}_2)(74)$	745	732
33	$\sigma(\text{CH}_3)(19)$		1487	1425	81	$\gamma(\text{OCCC})_{\text{phA}}(16),$ $\gamma(\text{NCCC})(14),$ $\gamma(\text{CCCC})(11)$	735	723
34	$\nu(\text{CC})_{\text{phB}}(10),$ $\sigma(\text{HCC})_{\text{phB}}(12)$		1482	1420	82	$\gamma(\text{NO}_2)(57)$	725	713
35	$\sigma(\text{HCC})_{\text{phB}}(21),$ $\nu(\text{CC})_{\text{phB}}(48)$		1458	1397	83	$\sigma(\text{CCC})_{\text{phA}}(23)$	717	705
36	$\nu(\text{N1C3})(12),$ $\sigma(\text{HOC})(16)$	1338	1453	1392	84	$\gamma(\text{OCCC})_{\text{phA}}(20),$ $\gamma(\text{NCCC})(29),$ $\gamma(\text{HCCC})(17)$	667	656
37	$\sigma(\text{HOC})(12),$ $\sigma(\text{HCC})(13)$		1423	1363	85	$\gamma(\text{CCCC})_{\text{phB}}(11),$ $\gamma(\text{NCCC})(13)$	663	652
38	$\sigma(\text{CH}_3)(58)$		1413	1354	86	$\sigma(\text{CCC})_{\text{phB}}(16)$	642	631
39	$\nu(\text{C=N})(11),$ $\sigma(\text{HC=N})(32)$		1399	1340	87	$\sigma(\text{ONC})(21),$ $\sigma(\text{NCC})(40)$	625	614
40	$\sigma(\text{HCC})(17),$ $\tau(\text{HCNC})(12)$		1388	1330	88	$\sigma(\text{CCC})_{\text{phA}}(21)$	582	572
41	$\nu(\text{CC})_{\text{phA}}(42)$		1382	1324	89	$\sigma(\text{CCC})_{\text{phA}}(10),$ $\sigma(\text{CNC})(13)$	562	552
42	$\sigma(\text{HCC})(10),$ $\tau(\text{HCNC})(40)$		1378	1320	90	$\gamma(\text{CCCC})_{\text{phB}}(14),$ $\gamma(\text{NCCC})_{\text{phB}}(13)$	556	547
43	$\nu_{\text{s}}(\text{NO}_2)(65)$	1319	1375	1317	91	$\sigma(\text{ONC})(28)$	534	525
44	$\nu_{\text{s}}(\text{NO}_2)(79)$	1302	1367	1310	92	$\sigma(\text{ONC})(29),$ $\sigma(\text{CNC})(17)$	508	499

45	$\nu(\text{CC})_{\text{phB}}(62)$	1349	1292	93	$\sigma(\text{ONC})(11),$ $\sigma(\text{NCC})(10)$	491	483	
46	$\nu(\text{OC})(11),$ $\tau(\text{CH}_2)(36),$ $\gamma(\text{HCNC})(22)$	1236	1340	1284	94	$\tau(\text{CCCC})_{\text{phA}}(14)$	481	473
47	$\sigma(\text{HCC})(30),$ $\tau(\text{HCNC})(21)$	1318	1263	95	$\tau(\text{CCCC})_{\text{phB}}(25),$ $\gamma(\text{NCCC})_{\text{phB}}(41)$	472	464	
48	$\nu(\text{C6C7})(12),$ $\sigma(\text{HC=N})(18)$	1293	1239	96	$\sigma(\text{OCC})(32)$	449	441	
				97	$\sigma(\text{CNC})(11),$ $\sigma(\text{CCN})(28)$	444	436	

^a Taken from Ref.[14]; ^b Potential Energy Distribution (PED) $\leq 10\%$ are not shown; ν , stretching; β , in-plane bending; γ , out-of-plane bending; ω , wagging; τ , twisting; σ , scissoring; δ , rocking; s, symmetric; as, asymmetric; ph, phenyl.

Table 3 Electronic properties of the studied compound

	B3LYP/6-311++G(d,p)
HOMO (eV)	-6.0076
LUMO (eV)	-3.2759
Energy gap (eV)	2.7317
Ionization potential	6.0076
Electron affinity	3.2759
Chemical hardness	1.3659
Chemical softness	0.7321
Chemical potential	-4.6418
Electrophilicity index	0.6830

Table 4 Experimental and calculated absorption wavelength, excitation energies, oscillator strengths and assignments in the acetonitrile solvent using the Time-Dependent DFT/B3LYP/6-311++G(d,p) method

Experimental ^a		TD-DFT/B3LYP		Major contributions	
λ (nm)	E (eV)	λ (nm)	f (a.u)	E (eV)	
		621.01	0.0048	1.9965	H $\pi\pi^*$ L(99%)
		553.23	0.0699	2.2411	H $\pi\pi^*$ L+1(99%)
		431.08	0.0011	2.8761	H $\pi\pi^*$ −1 L(100%)
		400.32	0.0018	3.0971	H $\pi\pi^*$ −1 L+1(99%)
413	3.0024	379.34	1.2337	3.2684	H $\pi\pi^*$ L+2(97%)
		357.44	0.0342	3.4687	H $\pi\pi^*$ −2 L(94%)

^aTaken from Ref.[14]

Table 6 Dipole moment μ (D), mean polarizability $\langle\alpha\rangle$ (in a.u. and esu), the anisotropic of the polarizability $\langle\Delta\alpha\rangle$ (in a.u.) and the mean first-order hyperpolarizability β (in a.u. and esu) values obtained using B3LYP/6-311++G(d,p) method

Parameters	B3LYP	Parameters	B3LYP	Parameters	B3LYP
μ_x	-11.0226	α_{xx}	543.274620	β_{xxx}	10056.9508749
μ_y	2.3100	α_{xy}	-7.646763	β_{xxy}	163.4117343
μ_z	1.1285	α_{yy}	261.904270	β_{xyy}	74.0111576
μ	11.3184	α_{xz}	4.581491	β_{yyy}	195.4884301
		α_{yz}	7.332379	β_{xxz}	313.8828316
		α_{zz}	153.741673	β_{xyz}	-244.2255195
		$\langle\alpha\rangle$ (a.u.)	319.6402	β_{yyz}	5.9875309
		$\langle\alpha\rangle\times 10^{-24}$ (esu)	47.3707	β_{xzz}	-200.4013089
		$\langle\Delta\alpha\rangle$ (a.u.)	348.8579	β_{yzz}	19.0287081
		$\langle\Delta\alpha\rangle\times 10^{-24}$ (esu)	51.7007	β_{zzz}	33.403582
				β (a.u)	9944.0268
				$\beta_{tot}\times 10^{-30}$ (esu)	85.9094
				β_{tot}/β_{urea}	110

Table 7 Binding Energies, Inhibition constants and Intermolecular energies of the studied Schiff base ligand against the coronavirus main protease

Compound	Binding Energy (kcal/mol)	Inhibition constant (M)	Intermolecular energy (kcal/mol)	Bond distances (Å)	Interaction Residues
6LU7					
DNP	-4.68	369.18	-7.07	3.3	PHE3
				2.1	ARG4
				5.6	LYS5
Favipiravir	-3.88	1.44	-4.47	3.8	THR11
				2.2	ASP295
Remdesivir	-3.45	2.95	-7.93	1.9	GLU290
				2.2	
				2.0	LYS5
				2.2	
				4.2	TYR126
Chloroquine	-4.62	410.16	-6.41	4.1	LYS-137
				5.5	TYR-126
				3.6	ASP-289
				3.0	GLU-288
				3.9	LYS-5

6LU7; 3-chymotrypsin-like protease

*

Due to technical limitations,Table 5 is only available as a download in the Supplemental Files section.

Figures

Figure 1

(left) the experimental geometry with atom-numbering scheme and (right) the optimize molecular structure obtained at DFT/B3LYP/6-311++G(d,p) level of theory for the (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol

Figure 2

View of the molecular Hirshfeld surfaces: the normalized contact distance, shape index and curvedness of DNP

Figure 3

The 2D fingerprint plots represent two di and de distances from the Hirshfeld surface to the nearest internal and external atoms, respectively

Figure 4

The comparison of experimental and computed FT-IR spectra of DNP

Figure 5

The computed 3D plots of HOMO-LUMO orbitals for the studied compound

Figure 6

The electrostatic potential mapped on molecular van der Waals surface (a) and area percent in each electrostatic potential range on the van der Waals surface (b) of the studied compound

Figure 7

Comparative UV-Vis spectrum using TD-DFT level of theory of DNP in the chloroform solvent

Figure 8

Critical point positions map of the (E)-5-(diethylamino)-2-((3,5-dinitrophenylimino)methyl)phenol

Figure 9

The two-dimensional scatter and coloured isosurface density representations illustrating the non-bonded interactions for DNP

Figure 10

The molecular docking results of DNP compound with the SARS-CoV-2 virus, including a 3-chymotrypsin-like protease.

Supplementary Files

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