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RESEARCH ARTICLE

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Investigate the interaction of testosterone/progesterone with ionic liquids on varying the anion to combat COVID-19: Density functional theory calculations and molecular docking approach

Kamlesh Kumari[1] | **Ajay Kumar**[2] | **Indra Bahadur**[3] | **Prashant Singh**[4]

[1]Department of Zoology, Deen Dayal Upadhyaya College, University of Delhi, New Delhi, India

[2]Department of Chemistry, Indian Institute of Technology, New Delhi, India

[3]Department of Chemistry, Faculty of Natural and Agricultural Sciences, North-West University, Mmabatho, South Africa

[4]Department of Chemistry, Atma Ram Sanatan Dharma College, University of Delhi, New Delhi, India

Correspondence
Prashant Singh, Department of Chemistry, Atma Ram Sanatan Dharma College, University of Delhi, New Delhi, India.
Email: psingh@arsd.du.ac.in

Ajay Kumar, Department of Chemistry, Indian Institute of Technology, New Delhi, India.
Email: ajayamuchem@gmail.com

Abstract

Hormones like testosterone and progesterone in the humans play significant role in the regulation of various biological processes like the body growth, reproduction, and others. In last two decades, researchers are using ionic liquids (ILs) extensively in different areas of sciences, and they are a novel class of compounds as well as their polarity can be tuned. ILs are multidisciplinary in nature and can be used in chemistry, materials science, chemical engineering, and environmental science. Further, ILs are being explored to increase the solubility of drugs or biological potential molecules. Testosterone and progesterone are found to be not very polar in nature; therefore, the authors attempt to increase the solubility of testosterone and progesterone via interaction with ILs. It was studied with density functional theory calculations using Gaussian, and an increase in the value of dipole moment is observed for the complex of testosterone/progesterone with the ILs in comparison of individual one. The optimization energy and other thermodynamic energies of the ILs (IL1-IL3), testosterone (T), testosterone-IL (T-IL1 to T-IL3), progesterone (P), and progesterone-ILs (P-IL1 to P-IL3) are found to be negative. Further, the change in free energy for the formation of complexes at room temperature is calculated. Further, the authors have investigated the synergistic effect of testosterone and progesterone against the main protease of new coronavirus using molecular docking. It is observed that the testosterone-**IL1** {IL1-3-(2-hydroxyethyl)-1-methyl-1H-imidazol-3-ium 2,4,6-trinitrophenolate} is found to be prominent against the main protease of SARS-CoV-2.

KEYWORDS

DFT calculations, ionic liquids, molecular docking, progesterone, testosterone

1 | INTRODUCTION

COVID-19 is the coronavirus diseases-19 and it occurs in humans due to the SARS-CoV-2. To date, millions of human deaths are reported globally.[1,2] The first case of 2019-nCoV was reported in China and then in different countries. This virus spread exponentially throughout the world, and the most affected countries from this virus are the United States, India, Brazil, and so forth. Initailly, the rate of spread of this infection was

low, but with passage of time, the rate of infection in humans increases rapidly.[3–8] The infection of COVID-19 may vary from person to person and mild to severe to acute. In mild cases, one may have little respiratory problems such as common cold, shortness of breath, and fever, whereas in severe or acute cases, one may suffer from acute pneumonia that may results in lung failure and also affect other organs of the human.[1–3,6,8,9] It is expected that this virus may interact with the sex hormones of humans like testosterone and progesterone, which play important role in regulation of different biological reactions in human beings like their growth, sexual activity, and others.[10–15] The solubility of testosterone and progesterone is not good; so to increase their solubility, ionic liquids (ILs) are being explored. Imidazolium, pyridinium, pyrrolidinium, piperidinium, ammonium bassed ILs are well investigated for different applications like green solvents, stabilization of biomolecules, extraction of compounds, and synthesis of nanomaterials and in the inhibition of the growth of the microorganisms. ILs are important in the biosciences and biotechnology for different interests. The interesting area for investigating ILs is the development of pharmaceutical applications as they can be used in solubilization of the biologically potentil molecules as well as in drug delivery. ILs are interesting as their polarity can be tuned by changing the cation/anion/alkyl chain. ILs are used in chemical and biological sciences, medicals, electrochemistry, and so forth. ILs are highly nonvolatile, nonflammable, and stable in air and water.[16–21] ILs are also reported to have promising antibacterial and antiviral potential. Computer-aided drug design (CADD) protocol is preliminary predictive model. Theoretical calculations have been performed to find promising candidates in less time. Density functional theory (DFT) approach is important to study the molecules for their chemical behavior in gaseous and in different solvents on different temperatures. Further, it can be used to know the feasibility of a reaction.[22–25] Screening and docking protocols are important tools in the designing and development of novel hit molecules. This approach is used to find best molecule based on binding energy (kcal/mol). Molecular docking is used to explore the potential of molecule against a receptor through different interaction and the interactions are studied using the physical data. AutoDock, ParDOCK, iGEMDOCK, and many others are used to explore the interactions through docking.[1,2,26–31]

Herein, the impact of the ILs on increasing the solubilities of the hormones (testosterone and progesterone) is studied using DFT calculations. Further, a synergistic effect of the hormones taken in presence of ILs with different anions was investigated against the main protease (Mpro) of novel coronavirus (nCoV) using the molecular docking.

2 | COMPUTATIONAL CALCULATIONS

2.1 | Designing of compounds

The structures of the hormones (testosterone and progesterone) and ILs were drawn using the ChemDraw as in Figure 1 and were utilized for the DFT calculations and the molecular docking. (http://www.cambridesoft.com).

2.2 | DFT calculations

DFT is a computer-based program to study the molecules used in physical sciences, chemical sciences, biology, and materials science. It is used to explore the behavior of the various system in particular atoms, molecules, and condensed phases. It is the most essential application in solid state physics for the calculations of electronic terms. In the 1990s, DFT was not considered to be accurate enough, but with passage of time, lots of improvements have been made to rely on the data obtained through DFT calculations.[32] The hormones (testosterone and progesterone) with and without ILs using DFT calculation using B3LYP method with the basis set 6-31G* using Gaussian software.[33–36] Using DFT calculations, various thermodynamic parameters like optimization energy, enthalpy, and free energy for the hormones (testosterone and progesterone), designed ILs, and their combinations were calculated. Further, different physiochemical descriptors are determined using the energy of frontier molecular orbitals. The representation of highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), and optimized geometry are extracted after the calculations.[26,37,38]

2.3 | Molecular docking

The molecular docking of designed candidates was performed into the cavity of target receptor, that is, Mpro of nCoV based on generic evolutionary method (GA) using iGEMDOCK software. Therefore, the GA parameters for molecular docking such as population size = 200, generations = 70, number of solutions = 2 are directly related to docking performance. The interaction of the hormones (testosterone and progesterone), designed ILs, and their combinations against the Mpro of SARS-CoV-2 are

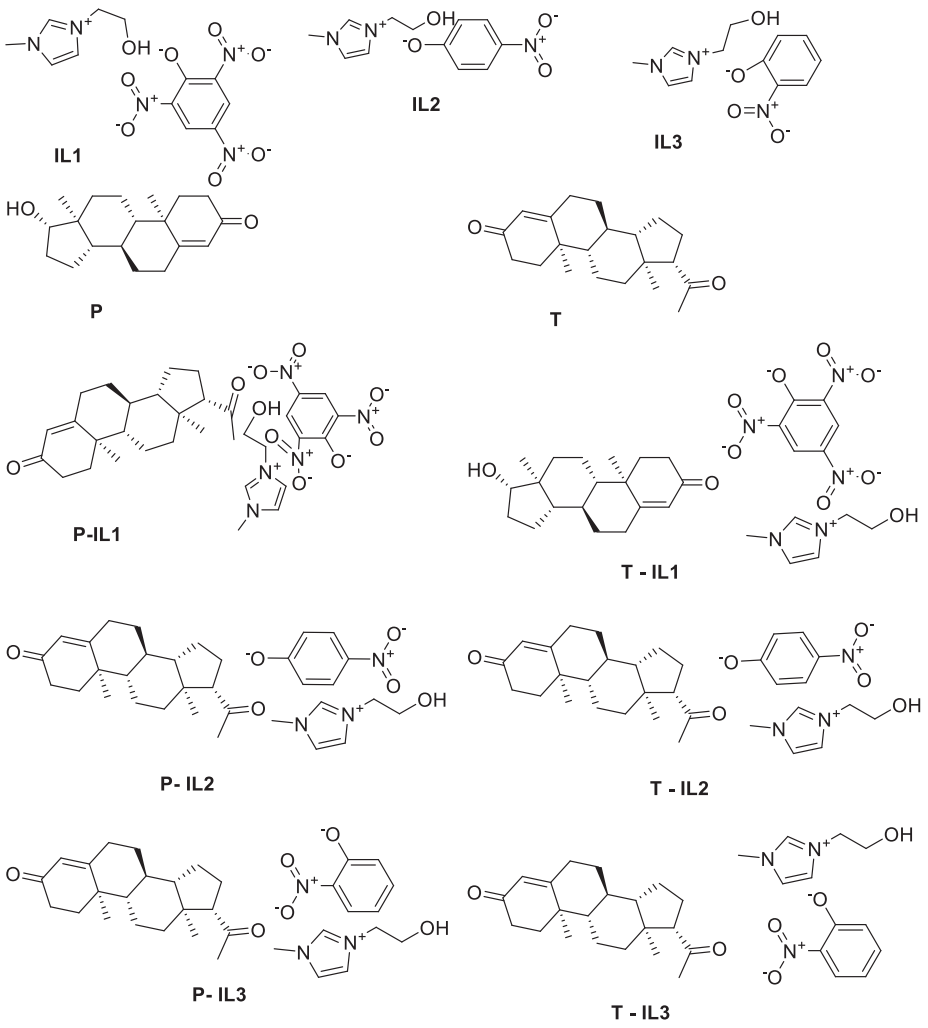

FIGURE 1 Structures of the designed ionic liquids (IL1-IL3), testosterone (T), progesterone (P), and the complexes (T-IL1, T-IL2, T-IL3, P-IL1, P-IL2, P-IL3)

IL1- 3-(2-hydroxyethyl)-1-methyl-1H-imidazol-3-ium 2,4,6-trinitrophenolate; IL2- 3-(2-hydroxyethyl)-1-methyl-1H-imidazol-3-ium 4-nitrophenolate; IL3- 3-(2-hydroxyethyl)-1-methyl-1H-imidazol-3-ium 2-nitrophenolate; P-Progesterone; T-Testosterone

performed to understand their individual effect and the synergistic or combined effect. iGEMDOCK, a computational tool was used to dock the designed molecules or compounds against the receptor of interest.[37,39–41] Before docking, the molecules should be optimized. The crystal structure of Mpro of nCoV (PDB: 6LU7) has been taken from the RCSB and prepared using the Chimera to make it error free; like addition, deletion of atoms has been done.[1,2,28–31]

3 | RESULT AND DISCUSSION

In this context, different frontier molecular orbitals, HOMO, LUMO, and their optimized geometry for the ILs, hormone (testosterone and progesterone), and their complexes have determined as in Figure S1, and HOMO, LUMO, and optimized geometry of only T-IL1 are given in Figure 2. It is used to understand the localization of electron density in different frontier molecular orbitals of molecules. It is expected that there may be changes in the locations of the electron density and that their energies of formation will vary.

Different thermodynamic parameters like optimization energy, zero-point energy, thermal energy, thermal enthalpy, and free energy of the ILs, hormones, and their complexes have been calculated in gasseous state as in in water at various temperature (298 K) as in Table 1. From these values, change in free energy for the formation of the complexes in gaseous state at temperature has been determined as in Table 2. Further, the energies of frontier molecular orbitals (HOMO and LUMO) were determined as in Table 3, and then using these energies, various physiochemical descriptors like $E_{HOMO} - E_{LUMO}$,

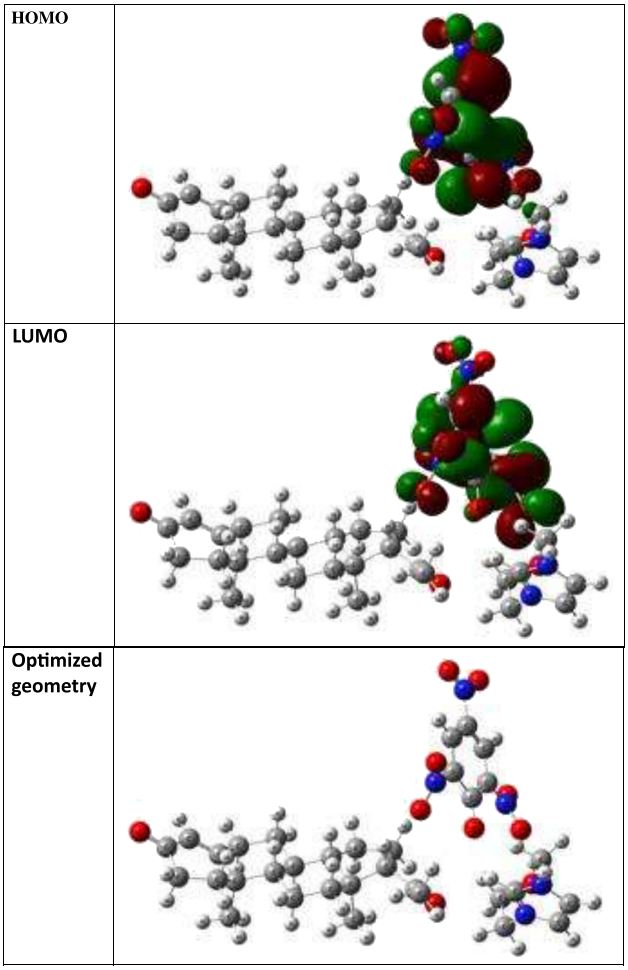

FIGURE 2 Representation of the frontier molecules orbitals (highest occupied molecular orbital [HOMO], lowest unoccupied molecular orbital [LUMO], and optimized geometry) of the T-IL1 as in Figure 1

$E_{HOMO} + E_{LUMO}$, chemical hardness (η), electronegativity (χ), softness (S), chemical potential (μ), and global electrophilicity index (ω), respectively, were calculated.

From Table 1, optimization energy, zero-point energy, thermal energy, thermal enthalpy, and free energy of the ILs, hormones, and their complexes have been calculated in gaseous state as in in water at room temperature can be investigated. All the energies for the ILs, testosterone/progesterone, and their complexes are negative. Further, for a better understanding for the formation of the complexes, the change in free energy for the formation of the complex between the hormones and ILs were calculated as given in Table 2 from the values given in Table 1. In Table 1, the values are calculated in Hartree per particle, and the values were converted in kcal/mol as in Table 2. The change in energy for the formation of complex for testosterone with IL3 is spontaneous as the value is negative while with ILs, it is zero. Further, the change in energy for the formation of complex for progesterone with IL1 is spontaneous at room temperature while it is positive for the complex with IL3, and with IL2, it comes out to be zero.

Dipole moment plays an important role to discuss the solubility of the compound. Herein, it can be seen that the dipole moment of the testosterone and progesterone is 2.3 and 4.49 debye, respectively, but on interaction with different ILs, a sharp increase in the dipole moment is observed, and it is also more than the respective ILs. Testosterone showed better interaction with the ILs and the dipole moment increases in synergistic approach.

Using DFT calculations, the energies of different frontiers molecular orbitals are determined and using the energy values of HOMO and LUMO, different important parameters are determined to understand the reactivity of the testosterone, progesterone, ILs, and their complexes. The parameters determined are chemical hardness (η), electronegativity (χ), softness (S), chemical potential (μ), and global electrophilicity index (ω) as in Table 3. It is considered that more the energy value of HOMO shows better capability to give the electron density and lesser the energy value of LUMO shows the ability to accept electron density. With decrease in the gap of FMO, chemical reactivity increases. Other parameters like polarizability, chemical potential, and electrophilicity are used to understand the reactivity of the molecule.

3.1 | Molecular docking

Molecular docking of the ILs (IL1-IL3), testosterone (T), testosterone-IL (T-IL1 to T-IL3), progesterone (P), and progesterone-ILs (P-IL1 to P-IL3) against the main protease of SARS-CoV-2 was performed using iGEMDOCK as in Table 4.[42] In reference to the data or results of molecular docking, it is clear that the designed ILs and hormones (testosterone and progesterone) showed good promising binding with the main protease of SARS-CoV-2 to avoid the infection. But, when the hormones (testosterone and progesterone) in the presence of ILS were docked against the main protease of SARS-CoV-2, the binding is better. In other words, it can be concluded that the inhibition of main protease of SARS-CoV-2 is enhanced. The best binding against the main protease of SARS-CoV-2 is observed with the complex of testosterone with IL1 i.e. testosterone-IL1.

The binding energy for the formation of the complex of testosterone and progesterone against the Mpro of nCoV are −79.40 and −84.30 kcal/mol. It is also important to know the binding energy for the formation of the complex of IL1, IL2, and IL3 against the Mpro of

TABLE 1 Various thermodynamics parameters (zero-point energy, thermal energy, thermal enthalpy, and thermal free energy) along with optimization energy and dipole moment of the ionic liquids (IL1-IL3), testosterone (T), testosterone-IL (T-IL1 to T-IL3), progesterone (P), progesterone-ILs (P-IL1 to P-IL3)

System	Sum of electronic and zero-point energies (Hartree/particles)	Sum of electronic and thermal energies (Hartree/particles)	Sum of electronic and thermal enthalpies (Hartree/particles)	Sum of electronic and thermal free energies (Hartree/particles)	Optimization energy (Hartree/particles)	Dipole moment (Debye)
IL1	−1340.42	−1340.40	−1340.40	−1340.48	−1340.70	15.5
IL2	−931.30	−931.29	−931.28	−931.35	−931.57	17.6
IL3	−931.32	−931.30	−931.30	−931.37	−931.59	9.6
T	−968.53	−968.51	−968.51	−968.58	−969.01	2.3
T-IL1	−2308.97	−2308.93	−2308.93	−2309.06	−2309.72	16.02
T-IL2	−1899.85	−1899.81	−1899.81	−1899.93	−1900.59	21.08
T-IL3	−1899.88	−1899.84	−1899.84	−1899.97	−1900.62	16.15
P	−891.12	−891.101	−891.10	−891.17	−891.56	4.49
P-IL1	−2308.97	−2308.93	−2308.93	−2309.06	−2232.26	12.2
P-IL2	−1822.45	−1822.41	−1822.41	−1822.52	−1823.16	16.4
P-IL3	−1822.44	−1822.40	−1822.40	−1822.52	−1823.15	11.7

TABLE 2 Change in formation for the formation of complexes between testosterone (T)/progesterone with the ionic liquids (IL1-IL3)

Change in energy for the formation of complex for testosterone			Change in free energy for the formation of complex for progesterone		
Complex	Hartree per particle	Kcal/Mol	Complex	Hartree per particle	Kcal/Mol
T-IL1	0.00	0.00	P-IL1	−77.41	−48,574.80
T-IL2	0.00	0.00	P-IL2	0.00	0.00
T-IL3	−0.02	−12.55	P-IL3	931.37	584,434.70

TABLE 3 Physiochemical descriptors of the ionic liquids (IL1-IL3), testosterone (T), testosterone-IL (T-IL1 to T-IL3), progesterone (P), and progesterone-ILs (P-IL1 to P-IL3)

C. No.	E_L	E_H	E_{H-L}	E_{L+H}	η	X	S	μ	Ω
IL1	−0.0949	−0.2259	−0.131	−0.3208	−0.0655	0.1604	−7.63359	−0.1604	−0.1964
IL2	−0.0562	−0.1747	−0.1185	−0.2309	−0.05925	0.11545	−8.43882	−0.11545	−0.11248
IL3	−0.056	−0.1863	−0.1303	−0.2423	−0.06515	0.12115	−7.6746	−0.12115	−0.11264
T	−0.0528	−0.2399	−0.1871	−0.2927	−0.09355	0.14635	−5.34474	−0.14635	−0.11448
T-IL1	−0.104	−0.2362	−0.1322	−0.3402	−0.0661	0.1701	−7.5643	−0.1701	−0.21887
T-IL2	−0.664	−0.1843	0.4797	−0.8483	0.23985	0.42415	2.084636	−0.42415	0.375033
T-IL3	−0.0718	−0.1967	−0.1249	−0.2685	−0.06245	0.13425	−8.00641	−0.13425	−0.1443
P	−0.0514	−0.2384	−0.187	−0.2898	−0.0935	0.1449	−5.34759	−0.1449	−0.11228
P-IL1	−0.0954	−0.2291	−0.1337	−0.3245	−0.06685	0.16225	−7.47943	−0.16225	−0.1969
P-IL2	−0.6158	−0.1757	0.4401	−0.7915	0.22005	0.39575	2.272211	−0.39575	0.355869
P-IL3	−0.0585	−0.1744	−0.1159	−0.2329	−0.05795	0.11645	−8.62813	−0.11645	−0.117

nCoV are −114.16, −85.95, and −96.06 kcal/mol. It is about the individual hormone or the IL. But considering the synergistic effect of hormones and ILs, an increase in binding energy for the formation of the complex is observed. Testosterone and progesterone showed maximum binding with Mpro of nCoV in the

TABLE 4 Binding energy of the ionic liquids (IL1-IL3), testosterone (T), testosterone-IL (T-IL1 to T-IL3), progesterone (P), and progesterone-ILs (P-IL1 to P-IL3)

S. No.	Compound/complex	$E_{Binding}$ (kcal/Mol)	E_{VDW} (kcal/Mol)	E_{HBond} (kcal/Mol)	E_{Elec} (kcal/Mol)
1	IL1	−114.16	−66.3253	−46.6226	−1.2117
2	IL2	−85.9528	−64.7713	−22.2463	1.06481
3	IL3	−96.0611	−63.9828	−32.9083	0.82998
4	Progesterone-IL1	−128.735	−92.7558	−34.6945	−1.28521
5	Progesterone-IL2	−111.432	−88.7699	−23.949	1.28673
6	Progesterone-IL3	−100.153	−79.5075	−20.6454	0
7	Progesterone	−84.3078	−83.2889	−1.01888	0
8	Testosterone-IL1	−134.491	−100.973	−35.8091	2.29099
9	Testosterone-IL2	−115.37	−87.7726	−26.0825	−1.51536
10	Testosterone-IL3	−106.117	−94.4118	−12.2167	0.512005
11	Testosterone	−79.4062	−73.4062	−6	0

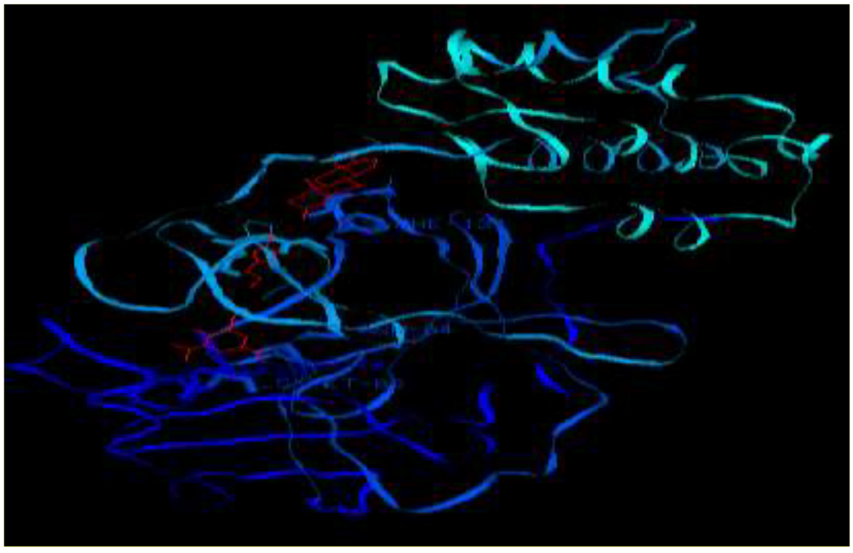

FIGURE 3 Docked view of testosterone-IL1 with Mpro of nCoV

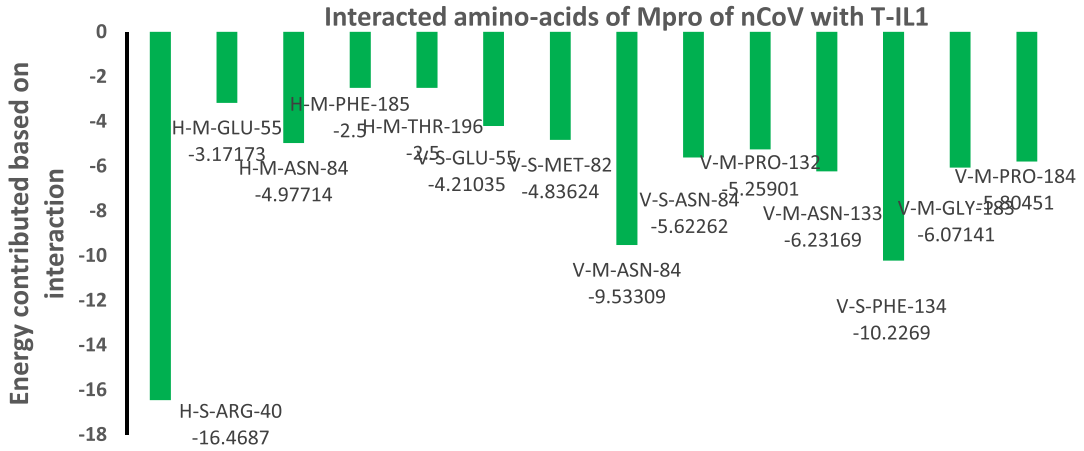

FIGURE 4 Interaction of T-IL1 with the amino-acids of Mpro of nCoV in terms of contributed energy

presence of IL1. Further, T-IL1 showed best binding energy with the Mpro of nCoV.[42]

The interaction of the complex, T-IL1 against the Mpro of nCoV through docking is given in Figure 3. It can be seen that the testosterone in presence of the IL1 interacts with different amino-acids of the Mpro of nCoV and the same can also be seen in Figure 4. It mainly interacts with Arg-40, Glu-55, Asn-84, Thr-196, Met-82, Pro-132, Asn-133, Phe-134, Gly-183, and Pro-184.

4 | CONCLUSION

In the present work, the authors have investigated the structural behavior of the hormones (testosterone and progesterone) in the presence/absence of different ILs with different anions using DFT calculation. Optimization energy and different thermodynamic energies of the ILs (IL1-IL3), testosterone (T), testosterone-IL (T-IL1 to T-IL3), progesterone (P), and progesterone-ILs (P-IL1 to P-IL3) are calculated and found to be negative, which indicates their stabilities. Further, the change in free energy for the formation of complexes at room temperature is calculated. Testosterone and progesterone are found to be nonpolar; therefore, testosterone and progesterone were interacted with ILs to increase the solubility. It was studied with the DFT calculations using Gaussian, and an increase in the value of dipole moment is observed for the complex of testosterone/progesterone and the ILs in comparison of individual one. Molecular docking against the Mrpo of nCoV was performed using iGEMDOCK, and binding energy for the formation of the complex is determined in kcal/mol. It is observed that the complex, testosterone and 3-(2-hydroxyethyl)-1-methyl-1*H*-imidazol-3-ium 2,4,6-trinitrophenolate found to be prominent against Mpro of nCoV.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

ORCID

Prashant Singh https://orcid.org/0000-0001-9648-2275

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