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Spectroscopic characterization of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea and assessment of reactive and optoelectronic properties employing DFT calculations and molecular dynamics simulations

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Abstract

IR and Raman spectra of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea (HIPPT) have been recorded in the solid phase and the vibrational wave numbers are calculated theoretically by B3LYP/6-31G(d,p) (6D, 7F) method. All the fundamental vibrational modes have been assigned using potential energy distribution values and the molecular structure was analyzed in terms of parameters like bond length, bond angles and dihedral angles. The ring breathing mode of the phenyl ring is observed at 1016 cm⁻¹ in the IR spectrum, 1014 cm⁻¹ in the Raman spectrum and at 1014 cm⁻¹ theoretically. The values of polarizability and hyperpolarizabilities were calculated and nonlinear optical properties are discussed. The HOMO-LUMO plot reveals the charge transfer possibilities in the molecule. The NBO analysis was computed and possible transitions were correlated with the electronic transitions. In the title compound, the imidazole ring and CH₂ groups are tilted from each other and the thiourea group is tilted from the phenyl ring. Using MEP plot the electrophilic and nucleophilic regions are identified. Local reactivity properties were investigated by

analysis of ALIE surfaces and Fukui functions. Oxidation and degradation properties were initially assessed by calculation of bond dissociation energies of all single acyclic bonds. Determination of atoms with pronounced interactions with water molecules was performed by calculation of radial distribution functions after molecular dynamics simulations. Charge hopping rates were calculated within Marcus semi-empiric approach, employing both DFT calculations and MD simulations. The molecular docking computational predictions were complemented by the *in vitro* antibacterial activity evaluation.

Keywords: DFT; Thiourea; RDF; ALIE; Optoelectronics; Docking.

1. Introduction

Emergence of multidrug resistance (MDR) amongst the bacteria has made the current chemotherapies less effective [1, 2]. The global report of WHO on antimicrobial resistance published in June 2014 reports that resistance of common bacteria to commercial antibiotics has reached alarming levels in many parts of the world. The report highlights that resistance to most widely used antibacterial medicines, fluoroquinolones and methicillin for the treatment of infections caused by *E. coli* and *S. aureus* respectively is very widespread [3]. This scenario poses a huge challenge for developing new classes of antibiotics which could be effective against the resistant microbial strains either because of higher inhibitory nature or due to different mechanism of action. Thiourea derivatives are versatile molecules which are capable of coordinating with metal ions and binding with biological targets to form stable complexes [4-6]. Oxygen, nitrogen and sulfur contribute in such bonding and increase the chances of thiourea derivatives binding with different biological receptors. The need for new chemotherapies for cancer and infectious diseases has motivated many researchers to use thiourea in combination with other moieties to design drugs for such diseases [7, 8]. Imidazole is a versatile ring with paramount biological importance [9-12] which is evident from the fact that it constitutes skeleton of many commercial drugs like metronidazole (antimicrobial), imidazole (antifungal) drugs, cimetidine (histamine H₂-receptor antagonist) and flumazenil (GABA_A receptor antagonist). Imidazole polyamides constitute a highly active structural group which shows anti-cancerous properties by binding at DNA minor groove [13, 14]. Combining multiple pharmacophoric units into a single molecule has been a successful method to design new drug candidates in structure based drug design [15]. Thiourea and its derivatives are versatile precursor units in the synthesis of many useful heterocyclic compounds [16]. Vibrational spectroscopic studies of certain thiourea derivatives are reported in literature [17-19]. Many thiourea materials with good NLO effects

have been designed and synthesized [20-25]. In the present work a complete vibrational analysis of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea (HIPPT) has been performed by combining the experimental Raman, IR spectral data and the quantum chemical calculations. In order to investigate the relationship between molecular structure and NLO response, the study is extended to determine the polarizability values.

Humankind is facing serious problems regarding the environmental pollution. Various chemicals are now used for the treatment of plants and soil while exhaust gases pollute atmosphere. Besides mentioned factors that threaten the environment, pharmaceutical compounds based on biologically active molecules are also emerging pollutants and since they have been detected in all types of water it is necessary to find economical and efficient mechanisms for their degradation and eventual removal [26-28]. This is serious challenge because biologically active molecules are synthesized to be stable, so they are able to perform their activity within the organism.

There are two main degradation mechanisms that are important from the aspect of practical applications; hydrolysis and oxidation [29, 30]. Beside degradation, understanding of hydrolysis is important from pharmaceutical aspect, as well. On the other side advanced oxidation processes are seen as both economical and efficient techniques for the degradation of organic pollutants [31]. Studies of degradation of biologically active molecules are long and tedious, but what matters most is that both of these mechanisms can be initially tested employing the combination of DFT calculations and molecular dynamics (MD) simulations. Therefore, this study also encompasses calculations of bond dissociation energies (BDE) of hydrogen abstraction, in order to determine the possible locations for autoxidation, and calculations of radial distribution functions (RDF) after MD simulations, in order to determine which atoms are having pronounced interactions with water.

Continuing our effort to build novel biologically active molecules [32, 33] herein, we applied a rational approach to design novel imidazole linked thiourea hybrid molecules. With this structural framework the activity is expected to exhibit multiple fold enhancements. Computational techniques to predict stability of an organic molecule are highly desirable to predict the effectiveness of a drug molecule in bio-systems. *Ab initio* DFT approach was used to predict stability of the synthesized thiourea derivative.

2. Experimental details

General procedure for the synthesis of 1-(3-(1H-imidazol-1-yl)propyl)-3-phenylthiourea

Phenylisothiocyanate (15 g, 111.11 mmol) was dissolved in chloroform and equimolar amount of amine (13.89 g, 111.11 mmol) was added slowly at room temperature, and then refluxed for 8 hours when precipitation of the product started. The precipitate was collected by filtration, washed with chloroform, and dried to afford product the title compound as white powder. The reaction mixture was poured on crushed ice and the separated solid product was filtered, washed with water, dried, and recrystallized from ethanol (95%). The crystals were purified by column chromatography using chloroform–methanol (4:1) as eluent to afford the title compound. The formation of title compound (Scheme) was confirmed by recording its FT-IR, ^1H -NMR, ^{13}C -NMR and HRMS spectra. ^1H -NMR and ^{13}C -NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer at 400 MHz with DMSO as solvent.

Infrared spectrum (Fig.S1-supporting information) was recorded on a Fourier transform infrared (FT-IR) spectrophotometer (Shimadzu model 8400 S) with a resolution of 2 cm^{-1} and in the range $400\text{--}4000\text{ cm}^{-1}$. The Laser-Raman spectrum (Fig.S2-supporting information) was recorded on Renishaw instrument using 633 nm line of Ne laser as excitation wavelength in the range $0\text{--}4000\text{ cm}^{-1}$ with spectral resolution of 2 cm^{-1} .

3. Computational details

Calculations of the title compound were carried out with Gaussian09 software [34] program B3LYP/6-31G(d,p) (6D, 7F) basis set to predict the molecular structure and vibrational wave numbers. The DFT method tends to overestimate the fundamental modes, therefore a scaling factor of 0.9613 has to be used for obtaining a considerably better agreement with experimental data [35] and the optimized geometrical (Fig.1) parameters are given in Table 1. The assignments of the calculated wave numbers were aided by GAUSSVIEW program [36] and potential energy distribution analysis [37].

Jaguar 9.0 [38] program, as implemented in Schrödinger Materials Science Suite 2015-4 [39], was used for DFT calculations of average local ionization energy (ALIE) surface, Fukui functions, bond dissociation energies (BDE) and optoelectronic properties which encompass hole and electron reorganization energies and transfer integrals. In all DFT calculations B3LYP exchange-correlation functional has been used with 6-311++G(d,p) basis set for ALIE surface, 6-31+G(d) for Fukui functions, 6-311G(d,p) for BDE, MIDIX for reorganization energies and 6-31G(d,p) for transfer integrals/charge coupling. For the calculations of reorganization energies screening method was used with empirical corrections based on results for many representative OLED molecules.

Desmond [40-43] program, also as implemented in Schrödinger Materials Science Suite 2015-4, was used for molecular dynamics (MD) calculations with optimized potential for liquid simulations (OPLS) 2005 force field [44] and with NPT ensemble class. The pressure was set to 1.0325 bar and temperature was set to 300 K, while simulation time was 5 ns, with cut-off radius of 12 Å. NVT ensemble class was used in the first 100 ps of simulation in order to relax the system. One molecule of HIPPT was placed in the cubic box with ~3000 water molecules and the solvent was treated with simple point charge (SPC) model [45].

In order to simulate amorphous phase for calculations of charge hopping rates, 32 molecules of HIPPT were placed in the cubic box and were simulated with OPLS 2005 force field for 10 ns at temperature of 300 K and pressure of 1.0325 bar with cut-off radius of 12 Å. Same procedure was conducted for thiourea molecule as well but, due to the fact that it is much smaller molecule than HIPPT, 256 molecules were placed in the cubic box. The method of Johnson was used for the analysis of non-covalent interactions [46, 47]. BDEs have been calculated for all single acyclic bonds.

4. Results and discussion

4.1 Geometrical parameters

The C-C bond lengths in the phenyl ring are in the range 1.3927-1.4041 Å and the bond lengths are somewhere in between the normal values for a single (1.54 Å) and a double bond (1.33 Å) [48]. The NH bonds are oriented away from the C-S bond so as to reduce the repulsive forces. Panicker et al. [19] reported the bond lengths $N_1-C_{19} = 1.3814$ Å, $N_{20}-C_{19} = 1.3814$ Å, whereas in the present case, the corresponding values are 1.3559, 1.3746 Å which are shorter than the C-N single bond of 1.4725 Å. The $C_{21}-N_{20}$ bond length for the title compound is 1.4168 Å formally a single bond, which is also remarkably shortened and the corresponding reported value is 1.4188 Å [19]. The partial double bond character of this structure is presumed as a result of the intra-molecular H-bond “locking” the molecule into a planar six-numbered ring structure. The C-S bond length in the present study 1.6869 Å lies between the values of C-S single and double bonds and the reported C-S bond length is 1.6636 Å [19]. Dilovic et al. [49] reported the bond lengths, $C_{19}-S_{23} = 1.6792$ Å, $C_{19}-N_{20} = 1.3422$ Å, $C_{19}-N_1 = 1.3462$ Å, $C_{21}-N_{20} = 1.4122$ Å, the bond angles, $C_9-N_1-C_{19} = 129.7^\circ$, $N_1-C_{19}-N_{20} = 114.3^\circ$, $N_1-C_{19}-S_{23} = 116.8^\circ$, $S_{23}-C_{19}-N_{20} = 128.8^\circ$, $C_{19}-N_{20}-C_{21} = 130.7^\circ$, $N_{20}-C_{21}-C_{26} = 124.7^\circ$ which are in agreement with the corresponding values 1.6869 Å, 1.3746 Å, 1.3559 Å, 1.4168 Å, 124.0° , 116.4° , 124.4° , 119.4° , 130.0° , 118.5° for the title compound. According to Ramanathan et al. [50] $C_{19}-S_{23} = 1.7073$ Å, $C_{21}-N_{20} = 1.4450$ Å, $C_9-N_1 =$

1.4375 Å, $C_{19}-N_{20}-C_{21} = 127.8^\circ$, $C_{19}-N_1-C_9 = 125.5^\circ$, $N_{20}-C_{19}-N_1 = 117.3^\circ$, $N_{20}-C_{19}-S_{23} = 120.4^\circ$, $N_1-C_{19}-S_{23} = 122.2^\circ$ whereas the corresponding values in the present case are , 1.6869 Å, 1.4168 Å, 1.4568 Å, 130.0° , 128.6° , 124.0° , 119.4° and 124.4° . In the present case, the imidazole ring the bond angles of $N_4-C_3-N_2$ and $N_4-C_5-C_6$ are 112.5° and 110.8° , where the reported values are 113.1° and 110.0° [51] and 111.8° and 108.6° [52]. The bond length $C_3-N_4 = 1.3158$ Å of the title compound shows typical double bond characteristics. However, $N_4-C_5 = 1.3770$ Å, $N_2-C_6 = 1.3821$ Å, $C_3-N_2 = 1.3689$ Å bond length of the title compound are shorter the normal C-N single bond of about 1.48 Å, where the reported values are 1.407 Å, 1.3950 Å, 1.3874 Å [51, 53] and 1.4179 Å, 1.3999 Å, 1.3908 Å [52]. The shortening of the C-N bond lengths of the title compound reveal the effects of resonance in this part of the molecule [54] and this situation can be attributed to the difference in hybridization of the different carbon atoms. The bond length $C_6=C_5$ is 1.3729 Å which is in agreement with the reported values 1.3830 Å [52] and 1.3827 Å [55]. At N_2 position of the title compound, the bond angles, $C_6-N_2-C_3 = 106.3^\circ$, $C_6-N_2-C_7 = 126.9^\circ$, $C_3-N_2-C_7 = 126.8^\circ$ and this asymmetry in angles is due to the steric repulsion between the CH_2 groups and imidazole ring. At C_{21} position the bond angles $C_{25}-C_{21}-C_{26}$ is reduced by 0.7° , $C_{25}-C_{21}-N_{20}$ is increased by 2.1° and $C_{26}-C_{21}-N_{20}$ is reduced by 1.5° from 120° which is due to the interaction between the phenyl ring and thiourea part. At N_{20} position, the bond angles are $C_{19}-N_{20}-C_{21} = 130.2^\circ$, $C_{19}-N_{20}-H_{22} = 112.4^\circ$, $C_{21}-N_{20}-H_{22} = 117.4^\circ$ and at N_1 the bond angles are $C_9-N_1-C_{19} = 124.0^\circ$, $C_9-N_1-H_{24} = 117.1^\circ$, $C_{19}-N_1-H_{24} = 117.4^\circ$ which are due to the steric repulsion between the different parts of the thiourea group. The imidazole ring and CH_2 groups are tilted from each other as is evident from the torsion angles, $C_5-C_6-N_2-C_7 = -177.4^\circ$, $C_6-N_2-C_7-C_8 = 73.5^\circ$, $N_4-C_3-C_7-C_8 = 177.5^\circ$ and $C_3-N_2-C_7-C_8 = -103.1^\circ$. Similarly the thiourea group is tilted from the phenyl ring as is evident from the torsion angles, $C_{27}-C_{26}-C_{21}-N_{20} = -177.6^\circ$, $C_{26}-C_{21}-N_{20}-C_{19} = -137.6^\circ$, $C_{29}-C_{25}-C_{21}-N_{20} = 178.7^\circ$ and $C_{25}-C_{21}-N_{20}-C_{19} = 45.3^\circ$.

4.2 IR and Raman spectra

In the following discussion the phenyl ring and imidazole ring are designated as Ph and R and the calculated scaled wave numbers, observed IR, Raman bands and assignments are given in Table 2.

NH modes

In aromatic compounds the N-H stretching vibration appears in the region 3400 ± 40 cm^{-1} [56]. In the present case, the band at 3448 cm^{-1} in the IR spectrum with theoretical values 3486 cm^{-1} and 3453 cm^{-1} are assigned as the NH stretching modes. N-H group show

deformation bands at $1510\text{--}1500\text{ cm}^{-1}$ and $740\text{--}730\text{ cm}^{-1}$ [57]. For the title compound, the NH deformation modes are assigned at $1517, 1490, 511, 474\text{ cm}^{-1}$ in the IR spectrum, $1522, 508\text{ cm}^{-1}$ in the Raman spectrum and at $1514, 1486, 510, 478\text{ cm}^{-1}$ theoretically.

CH modes of the imidazole ring

The CH modes of the imidazole ring are observed at $3160, 3118\text{ cm}^{-1}$ (IR), $3152, 3119\text{ cm}^{-1}$ (Raman), $3156\text{--}3121\text{ cm}^{-1}$ (DFT) (stretching modes); $1260, 1101\text{ cm}^{-1}$ (IR), $1263, 1108\text{ cm}^{-1}$ (Raman), $1271\text{--}1058\text{ cm}^{-1}$ (DFT) (in-plane deformation modes) and at $825\text{--}700\text{ cm}^{-1}$ (DFT) (out-of-plane deformation modes) as expected in literature [56–59].

C=S, C=N, C-N, C=C modes

The C=S stretching bands are observed in the range $670\text{--}930\text{ cm}^{-1}$ and the deformations modes at $510 \pm 90\text{ cm}^{-1}$ and $420 \pm 100\text{ cm}^{-1}$ [56–59]. In the present case the DFT calculations give the stretching mode of C-S at 880 cm^{-1} and deformation modes at 605 and 563 cm^{-1} . The reported values of C-S stretching mode is at 908 cm^{-1} in IR, 911 cm^{-1} in Raman and 908 cm^{-1} (DFT) for a thiourea derivative [19]. The C=N stretching modes were reported in the range $1500\text{--}1666\text{ cm}^{-1}$ [58–60] and for an imidazole derivative, Benzon et al. [61] reported the C=N stretching mode at 1464 cm^{-1} theoretically and at around 1463 cm^{-1} experimentally. Benzon et al. [61] reported the CN stretching modes at $1247, 1129, 938\text{ cm}^{-1}$ theoretically, $1248, 1135, 926\text{ cm}^{-1}$ in the Raman spectrum and at 924 cm^{-1} in the IR spectrum. For the title compound, the CN stretching modes are assigned at $1329, 1215, 1101, 1004\text{ cm}^{-1}$ in the IR spectrum, $1482, 1350, 1324, 1108\text{ cm}^{-1}$ in the Raman spectrum and at $1484, 1372, 1344, 1325, 1220, 1213, 1141, 1105, 1007\text{ cm}^{-1}$ theoretically. Malek et al. reported the CN stretching modes of benzimidazolium salts at $1268, 1220, 1151\text{ cm}^{-1}$ theoretically [62]. The C=C stretching mode of the imidazole ring is assigned at 1496 cm^{-1} theoretically which is agreement with literature [58].

CH₂ modes

The stretching vibrations and deformations modes (scissoring, wagging, twisting and rocking) associated with the CH₂ group appears in the regions $3020\text{--}2855\text{ cm}^{-1}$ and $1450\text{--}850\text{ cm}^{-1}$ respectively [56, 59]. The bands at $3003, 2951, 2928\text{ cm}^{-1}$ in the IR spectrum, $3007, 2993, 2970, 2945, 2932\text{ cm}^{-1}$ in the Raman spectrum and modes in the range $3006\text{--}2030\text{ cm}^{-1}$ (DFT) are assigned as the stretching modes of CH₂ groups of the title compound. The deformation modes of the CH₂ groups are observed at $1458, 1444, 1417, 1360, 1047, 1022, 836\text{ cm}^{-1}$ in the IR spectrum and at $1444, 1382, 839\text{ cm}^{-1}$ in the Raman spectrum. The DFT calculations give these modes in the range $1457\text{--}835\text{ cm}^{-1}$ as expected.

Phenyl ring modes

The phenyl CH stretching modes are normally expected above 3000 cm^{-1} [56] and for the title compound, the DFT calculations give these modes in the range $3092\text{--}3062\text{ cm}^{-1}$ and experimentally bands are observed at 3094 , 3077 and 3055 cm^{-1} in the Raman spectrum. The ring stretching modes of the phenyl ring are assigned at 1596 , 1577 , 1444 , 1310 cm^{-1} in the IR spectrum, 1588 , 1444 cm^{-1} in the Raman spectrum and at 1593 , 1577 , 1475 , 1444 , 1305 cm^{-1} theoretically which are in agreement with literature [56, 63]. The ring breathing mode of the mono substituted phenyl ring is around 1000 cm^{-1} [56, 64] and in the present case the bands at 1016 cm^{-1} in IR, 1014 cm^{-1} in Raman and 1014 cm^{-1} (DFT) is assigned as the ring breathing mode of the phenyl ring. The in-plane and out-of-plane deformation modes of the phenyl ring are expected above and below 1000 cm^{-1} [56] and for the title compound, the bands observed at 1162 , 1071 , 1016 cm^{-1} in IR, 1165 , 1072 , 1014 cm^{-1} in Raman, $1287\text{--}1014\text{ cm}^{-1}$ (DFT) and 955 , 935 , 890 , 811 cm^{-1} in IR, 902 cm^{-1} in Raman, $960\text{--}734\text{ cm}^{-1}$ (DFT) are assigned as the in-plane and out-of-plane bending modes of the phenyl ring, respectively.

The RMS errors between the experimental and theoretical wave numbers are: 3.37 for IR bands and 5.19 for Raman bands.

4.3 ^1H and ^{13}C NMR spectra

For the title compound, the absolute isotropic chemical shielding was calculated by B3LYP/GIAO model [65] and relative chemical shifts were then estimated by using the corresponding TMS shielding: $\sigma_{\text{calc}}(\text{TMS})$ calculated in advance at the same theoretical level as this paper and numerical values of chemical shift $\delta_{\text{calc}} = \sigma_{\text{calc}}(\text{TMS}) - \sigma_{\text{calc}}$ together with calculated values of $\sigma_{\text{calc}}(\text{TMS})$, are given in Table 3.

^1H -NMR spectra of this compound showed two broad singlets which were interpreted for thiourea N-H at δ 7.7 and 9.5. The most prominent peaks in ^{13}C NMR spectra at δ 180 confirmed the presence of C=S linkage.

^1H NMR (δ , ppm, DMSO- d_6 , 400 MHz) δ 9.50 (s, 1H, ^{20}NH), 7.79 (s, 1H, ^1NH), 3.49 (t, 2H, $J=5$, $^9\text{CH}_2$), 2.02 (m, 2H, $^8\text{CH}_2$), 4.01 (t, 2H, $J=6.96$, $^7\text{CH}_2$), 7.62 (s, 1H, ^3CH), 6.89 (d, 1H, ^5CH), 7.14 (d, 1H, ^6CH), 7.4068 (dd, 2H, $J=7.44$, 1.04 Hz, $^{25,26}\text{CH-phenyl}$), 7.3048 (td, $J=8.28$, 7.44, 2H, $^{27,29}\text{CH-phenyl}$), 7.0956 (td, $J=7.36, 7.32$, 1H, $^{28}\text{CH-phenyl}$); ^{13}C NMR (δ , ppm, DMSO- d_6 , 125 MHz) δ 180.57 (^{19}C), 139.06 ($^{21}\text{C}_{\text{Ar}}$), 137.09 (^3C), 128.51 ($^{25,26}\text{C}_{\text{Ar}}$), 128.35 ($^{28}\text{C}_{\text{Ar}}$), 124.14 (^5C), 123.21 ($^{27,29}\text{C}_{\text{Ar}}$), 119.12 (^6C), 43.84 (^7C), 41.15 (^9C), 30.11 (^8C); HRMS ESI m/z $[\text{M}]^+ = 260.35351$.

The protons of the phenyl and imidazole rings resonate in the ranges, 7.2244-8.4891 ppm and 7.9273-8.1035 ppm theoretically. The circulation of the double bond electrons in a secondary magnetic field accounts for the formation of magnetic anisotropy. Therefore, chemical shifts of the hydrogen atoms of the CH₂ groups are 4.8214 (H13), 4.4131 (H14), 2.1368 (H15), 3.6771 (H16), 5.2623 (H17) and 3.7415 ppm (H18). The chemical shifts of the hydrogen atoms associated with nitrogen atoms are 7.9441 and 6.6544 ppm and these high values are due to electronegative nitrogen atoms.

For aromatic carbon atoms, the range of ¹³C NMR shifts are normally greater than 100 ppm [66, 67] and for the title compound, ¹³C NMR chemical shifts of the entire phenyl carbon atoms are greater than 100 ppm as expected in literature. The predicted shifts lie in the ranges 117.744-133.9391 ppm for the imidazole ring and 120.8894-136.6582 ppm for the phenyl ring. The chemical shifts of carbon atoms in the CH₂ groups are 50.4235 ppm (C₇), 39.0035 ppm (C₈), 48.2889 (C₉) and in the thiourea group is 180.3557 ppm (C₁₉). For the carbon atoms, C₁₉ the high chemical shift is due to the neighbouring nitrogen atoms.

4.4 Nonlinear optical properties

The increasing volume of information processing and communication in continuing to be a big challenge in the modern technology and now the use of organic materials in optoelectronics has increased dramatically [68]. To test the nonlinear optical response of the title compound, the finite field approach has been implemented and based on the finite field approach the nonlinear optical parameters such as dipole moment, polarizability, the first and second order hyperpolarizability of the title compound are calculated using B3LYP/6-31G(d,p) (6D, 7F) basis set level. For the title compound, polarizability and first hyperpolarizability are 2.6607×10^{-23} esu and 4.5533×10^{-30} esu and the first hyperpolarizability is 35.03 times that of the standard NLO material urea [69]. The reported values of hyperpolarizability of similar derivatives are 2.55×10^{-23} esu [36], 2.7×10^{-23} esu [50] and 2.24×10^{-23} esu [70]. Second hyperpolarizability of the title compound is calculated by using the equation $\gamma_{av} = 1/5[\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz}]$ and the value is -20.155×10^{-37} esu.

4.5 Molecular electrostatic potential

Molecular electrostatic is widely used as a tool for interpreting potentials and predicting the reactive behaviour of a wide variety of chemical systems, the study of biological recognition processes and hydrogen bonding interactions [71]. The molecular electrostatic potential was calculated at B3LYP/6-31G(d,p) (6D, 7F) level of theory to predict

reactive sites for electrophilic and nucleophilic attack for the investigated compound. The different values of the electrostatic potential at the surface are represented by different colours; red represents region of most electronegative electrostatic potential, blue represents region of the most positive electrostatic potential and green represent region of zero potential. Potential changes in the order red < orange < yellow < green < blue. The MEP surface provides necessary information about the reactive sites and the total electron density on to which the MEP has been mapped is shown in Fig. S3 (supporting information). This figure provides a visual representation of the chemically active sites and comparative reactivity of atoms [72]. From the MEP plot, the nitrogen atom N₄ of the imidazole ring and sulphur atom S₂₃ are the electrophilic regions and NH groups represent the nucleophilic regions. The electrophilic reactivity is related to negative region and the nucleophilic reactivity is to positive one as can be seen from the MEP of the candidate molecule.

4.6 ALIE surfaces and Fukui functions

MEP allows one to perform initial assessment of molecule's local reactivity based on the charge distribution. However, ALIE surface allows better determination of molecule sites prone to electrophilic attacks, because it indicates the locations where electrons are least tightly bound and therefore most easily removed, i.e. molecule areas that are most reactive towards electrophiles. This important quantum molecular descriptor was introduced by Sjoberg et al. [73, 74] and is defined as following:

$$I(r) = \sum_i \frac{\rho_i(\vec{r}) |\epsilon_i|}{\rho(\vec{r})}, \quad (1)$$

where $\rho_i(\vec{r})$ represents the electronic density of the i -th molecular orbital at the point $\vec{r}$, ϵ_i represents the orbital energy and $\rho(\vec{r})$ is the total electronic density function. This quantum molecular descriptor is particularly useful when its values are mapped to the electron density surface, which is for HIPPT molecule represented in Fig.2. Red colour in Fig.2 indicates the location of HIPPT molecule where electrons are least tightly bound. This location is fully located around the sulfur atom so it can be concluded that this atom is prone to be under electrophilic attack. Purple colour of ALIE surface also indicates that electrons located around hydrogen atom H22 are the most tightly bound.

Analysis of intra-molecular non-covalent interactions reveals one such interaction, Fig.2, located between carbon atom H24-C25, which probably influences rotation possibilities of bonds between atoms N20-C21 and C19-N20.

Fukui functions also turned out to be very useful in order to gain deeper insight into the local reactivity properties of molecules. The definition of Fukui functions based on finite difference approach involves two following equations:

$$f^+ = \frac{(\rho^{N+\delta}(r) - \rho^N(r))}{\delta}, \quad (2)$$

$$f^- = \frac{(\rho^{N-\delta}(r) - \rho^N(r))}{\delta}, \quad (3)$$

where N denotes the number of electrons in the reference state of the molecule and δ represents the fraction of electron, which is set to be 0.01. This value yielded results which are in agreement with other results [75].

Fukui functions indicate the changes of electron densities after addition or removal of charge, so important conclusions can be made on the molecule's reactivity when it is subjected to nucleophilic or electrophilic attack. In this work the values of Fukui f^+ and f^- functions have been mapped to electron density surface in such manner that in case of f^+ function purple colour (positive colour) denotes locations where molecule gains in electron density when it is subjected to nucleophilic attack, while in case of f^- function red colour (negative colour) denotes locations where molecule loses electron density when it is subjected to electrophilic attack.

According to the results presented in Fig.3 it can be seen that concerning the f^+ functions carbon atoms of benzene ring are seen as possible reaction center as significant amount of electron density is gained at those locations as a consequence of nucleophilic attack. Similar conclusion can be drawn for the area in near vicinity of sulfur atom. On the other side it can be seen in Fig.3 that HIPPT molecule loses electron density in the area between benzene ring and nitrogen atom, when it is under electrophilic attack.

4.7 Frontier molecular orbital analysis

To explain several types of reactions and for predicting the most reactive position in conjugated systems, molecular orbital, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and their properties such as energy as widely used [76]. The given values of HOMO and LUMO and the HOMO-LUMO energy gap reflect the biological activity of a molecule. A molecule having a small energy gap is more polarisable and is generally associated with a high chemical reactivity and low kinetic stability [77, 78]. HOMO is the outer orbital containing electrons and tends to give these electrons as an electron donor and hence the ionization potential is directly related to the

energy of the HOMO while the LUMO can accept electrons and the LUMO energy is directly related to electron affinity [79, 80]. From Fig.S4, the HOMO-LUMO plot, it is very clear that the HOMO is localized over the thiourea group, while the LUMO is over the thiourea and phenyl ring and there is a possibility of charge transfer in the system through these regions. For the title compound, $E_{\text{HOMO}} = -5.743$ eV and $E_{\text{LUMO}} = -0.952$ eV. Ionization potential, I , electron affinity, A , electronegativity, χ , global hardness, η , chemical potential, μ and global electrophilicity index, ω , [79-81] were calculated using the equations, $I = -E_{\text{HOMO}} = 5.743$, $A = -E_{\text{LUMO}} = 0.952$, $\chi = -(E_{\text{HOMO}} + E_{\text{LUMO}})/2 = 3.3475$, $\eta = (I - A)/2 = 2.3955$, $\mu = -(I + A)/2 = -3.3475$ and $\omega = \mu^2/2\eta = 2.3389$. Global electrophilicity index measures the stabilization energy when the system acquires an additional electronic charge from the environment. Electrophilicity compasses both the ability of an electrophile to acquire additional electronic charge and the resistance of the system to exchange electronic charge with the environment. It contains information about both electron transfer (chemical potential) and stability (hardness) and is a better descriptor of global chemical reactivity.

4.8 Natural Bond Orbital Analysis

The natural bond orbitals (NBO) calculations were performed using NBO 3.1 program [82] as implemented in the Gaussian09 package at the DFT/ B3LYP/6-31G(d,p) (6D, 7F) level in order to understand various second-order interactions which are given in Tables 4 and 5. NBO analysis provide an efficient method for studying interesting features of molecular structure, intra and inter molecular bonding and the bond interactions charge transfer or conjugative interactions in molecular system [83]. Also NBO analysis gives information about interactions in both filled and virtual orbital spaces that could enhance the analysis of intra and intermolecular interactions [84]. The strong interaction $n_1N_2 \rightarrow \pi^*(C_3-N_4)$ has the highest stabilization energy value, 47.41 kJ/mol. A very strong interaction has been observed between the $\pi(C_{21}-C_{25})$ and $\pi^*(C_{28}-C_{29})$ with a stabilization energy of 20.55 kJ/mol. Table 5 gives the occupancy of electrons and p-character [85] in significant NBO natural atomic hybrid orbitals. Almost 100% p-character was observed in lone pairs of N_1 , N_2 , N_{20} and S_{23} . Similarly, 100% p-character was observed in π bonding of C_5-C_6 .

4.9 Reactive properties based on autoxidation and hydrolysis

DFT calculations can be used for initial assessment of degradation properties of some molecule and in such way contribute to the overall rationalization and optimization of experiments. Namely, calculations of BDE for hydrogen abstraction allow prediction of possible molecule sites that are prone to oxidation. Namely, if the BDE of hydrogen

abstraction at certain site of molecule is within the proper range, then that location is candidate for autoxidation process to start. Formation of a radical of pharmaceuticals occurs together with formation of peroxy radical [86] and reaction can proceed further if the formed peroxy radical can abstract hydrogen from another pharmaceutical molecule. As previously mentioned that hydrogen can be abstracted only at certain positions, for which the BDE of the hydrogen in the pharmaceutical molecule is lower than the BDE of the peroxide [87], while all peroxy radicals have similar BDE values which are in the range of 87 kcal/mol to 92 kcal/mol. These values are independent of the chemical surrounding [86, 88] and if the calculated BDE of hydrogen abstraction at some position is close to this interval, that position can be considered as a possibly prone to oxidation. Wright et al. [89] stated that lower border of this interval could be around 75 kcal/mol, while for values lower than 70-75 kcal/mol, autoxidation is not probable [86, 89]. In this study BDEs of all single acyclic bonds have been calculated for the HIPPT molecule. Results are presented in Fig.4.

BDE for hydrogen abstraction are given in red colour, while BDE for the rest of the single acyclic bonds are given in blue colour. According to presented results BDE of only one bond is having value which is just close to the upper border for autoxidation to occur. That is bond denoted with number 9, with BDE value of ~93kcal/mol. This indicates that HIPPT molecule could be very stable in open air and in presence of oxygen. On the other side, the lowest BDE has been calculated for the bond 18, with the value of 73kcal/mol, indicating that degradation process could start here.

To investigate which atoms of molecule HIPPT are having pronounced interactions with water molecules we are further referring to the RDF, as calculated after MD simulations. RDF, $g(r)$, represents the probability of finding a particle in the distance r from another particle [90]. The profile and peak distance of RDF curve are the crucial parameters that indicate to what extent is some molecule's atom prone to interactions with water molecules. Sharpe RDF curve with short distance of peak indicate significant interactions with water molecules. Results presented in Fig.5 indicate that atoms N2, N4, C5, H22 and S23 are having significant interactions with water molecules, comparing with rest of the atoms of HIPPT molecule. Taking into account the peak distance, the most significant interaction with water is having hydrogen atom H22, with peak distance of somewhat less than 2 Å and $g(r)$ value of ~0.7. Nitrogen atom N4 is having larger value of $g(r)$, ~0.95, but on the higher peak distance which is having value of somewhat less than 3 Å. N4, however, is having two distinct solvation spheres, with the second one being located ~4,5 Å. Atoms C5 and S23 are

having similar RDF curves, with peak distances close to 3.5 Å and $g(r)$ value of ~1.2. The largest $g(r)$ value of ~1.3 is having atom N2, but in this case peak distance is also the highest with the value of ~4.5 Å.

4.10 Charge transfer rates between HIPPT molecules

The motivation for the investigation of charge transfer rates between HIPPT molecules we found in the fact that this molecule is based on thiourea. Thiourea is analogue of urea molecule, where one carbon atom is replaced with sulfur atom. Urea, on the other side, serves as a material with reference value of hyperpolarizability - a quantity that resembles potential for practical application as NLO material. Thus, we have compared the optoelectronic properties of thiourea and HIPPT molecule.

Transfer of electrons and holes between organic molecules at room temperature is treated by the so called hopping mechanism which is quantified by semi-empiric approach of Marcus through following convenient expression [91, 92]:

$$k_{ET} = \frac{4\pi^2}{h} \frac{1}{\sqrt{4\pi\lambda k_B T}} t^2 \exp\left[\frac{-\lambda}{4k_B T}\right]. \quad (4)$$

k_{ET} represents the charge hopping/transfer rate and is directly proportional to diffusion coefficient and mobility of charge carriers, so its determination allows one to initially assess the charge transport properties of some molecule within the hopping mechanism. Analyzing equation (3) one concludes that two quantities principally determine the values of k_{ET} . Those quantities are electron/hole reorganization energy (λ_-/λ_+) and transfer integral (also known as charge coupling, t). In order to achieve high values of k_{ET} , λ_-/λ_+ should be minimized, while t should be maximized. Reorganization energies are related to charge injection properties, while charge coupling is related to the orbital overlap between molecules. Reorganization energies have been calculated using equations:

$$\lambda_1 = E^0(G^*) - E^0(G^0), \quad (5)$$

$$\lambda_2 = E^*(G^0) - E^*(G^*), \quad (6)$$

$$\lambda_i = \lambda_1 + \lambda_2 \quad (7)$$

where $E^0(G^0)$ and $E^*(G^*)$ stand for the ground state energies of the neutral and ionic states, respectively, $E^0(G^*)$ is the energy of the neutral molecule at the optimal ionic geometry, while $E^*(G^0)$ is the energy of the charged state at the optimal geometry of the neutral

molecule. Charge transfer integral has been calculated using dimer frontier orbital splitting approximation.

We have firstly calculated reorganization energies of thiourea and HIPPT molecules. Then, their amorphous phases were modeled by MD simulations as mentioned in the Computational details chapter. In cases of both thiourea and HIPPT molecules, half of all pairs within 4 Å distance were randomly picked from the last snapshot of MD simulation for calculations of t and k_{ET} . Average values of t and k_{ET} were taken and all results are presented in Table 6. Similar approach was also employed in work by Evans et al. [93].

Brief look at reorganization energies indicate that HIPPT molecule should have significantly better charge hopping properties than thiourea molecule, because it has significantly lower values of reorganization energies. Namely, λ_- decreased from 0.80 eV to 0.67 eV, while λ_+ decreased from 0.33 eV to 0.21 eV, in favor of HIPPT molecule. Indeed, HIPPT molecule is having better charge hopping properties, but not to the expected extent. This indicates that interaction between HIPPT molecules is weaker than in case of thiourea molecules, which is in agreement with values of t , which has average values of 0.15 and 0.08 for thiourea and HIPPT molecules, respectively. So, the orbital overlap between HIPPT molecules is smaller than between thiourea molecules, but reorganization energies are lower so there is certain improvement of k_{ET} . k_{ET}^- is practically the same for both molecules, 2.92×10^{11} for thiourea and $2.96 \times 10^{11} \text{ s}^{-1}$ for HIPPT, while k_{ET}^+ of HIPPT is 80 % better than for thiourea, $3.65 \times 10^{13} \text{ s}^{-1}$ for HIPPT comparing with $2.01 \times 10^{13} \text{ s}^{-1}$ for thiourea.

4.11 In vitro antimicrobial assay

Disk diffusion susceptibility method [94] in accordance with National Committee for Clinical Laboratory Standards (NCCLS) guidelines was employed to investigate antibacterial activity of the compounds against some Gram positive (*B. subtilis*, MTCC No 10619 and *S. aureus*, MTCC No 96), and Gram negative bacteria (*P. aeruginosa*, MTCC No 1748 and *E. coli*, MTCC No 68). Pure microbial strains were obtained from MTCC IMTECH, Chandigarh, India. Mueller-Hinton agar purchased from HiMedia, India, was melted and subsequently poured (20mL) into Petri plates (100 mm). It was kept undisturbed at room temperature to solidify. A representative sample of the media was kept at 37 °C in BOD incubator for 24 hours to check the sterility. The culture of each bacterium in saline was uniformly spread over the media with a cotton swab. Sterile filter paper discs of 6 mm diameter, impregnated with respective concentrations of compounds (in DMSO) were applied

to the surface of inoculated plates. The plates were kept in BOD incubator for 24 hours at 37°C and subsequently examined for bacterial growth. As is obvious from the Fig. S5 (supporting material), the compounds possess broad spectrum activity against four different microbial strains. The highest inhibition value was found for *B. subtilis* followed by *P. aeruginosa*, which suggests that the compound is highly effective against both Gram positive & Gram negative bacteria. The activity values were compared with standard drugs Streptomycin and Ciprofloxacin. As is evident from table 7, the compound HIPPT exhibited inhibition zones which are comparable to the standard reference drugs and in case of *B. subtilis*, compound HIPPT was more effective than the standard drugs streptomycin and Ciprofloxacin. The activity of standard drugs was reported in our earlier work [95].

4.12 Molecular Docking studies

High resolution crystal structure of ACP reductase was downloaded from the RCSB PDB website (PDB ID: 1QG6) [96]. All molecular docking calculations were performed on AutoDock-Vina software [97]. The protein was prepared for docking by removing the co-crystallized ligands, waters and co-factors. The AutoDockTools (ADT) graphical user interface was used to calculate Kollman charges and polar hydrogens. The ligand was prepared for docking by minimizing its energy with MMFF94s force field. Partial charges were calculated by Geistenger method. The active site of the enzyme was defined to include residues of the active site within the grid size of 40Å x 40Å x 40Å. The most popular algorithm, Lamarckian Genetic Algorithm (LGA) available in Autodock was employed for docking. The docking protocol was tested by extracting co-crystallized inhibitor from the protein and then docking the same. The docking protocol predicted the same conformation as was present in the crystal structure with RMSD value well within the reliable range of 2Å. Amongst the docked conformations, one which binds well at the active site was analyzed for detailed interactions in Discover Studio Visualizer 4. Docking study reveals that the synthesized molecules bind at the same site where the co-crystallized drug Triclosan is attached. (Fig. 6) Ala95 and Tyr156 form H-bonds of 2.27 and 2.34 Å lengths respectively with 3e (Fig. S6-supporting information). Tyr146 forms π - π interaction with phenyl ring of the molecule. These interactions together with other weak forces are responsible for formation of strong ligand-macromolecule complex. These findings predict that the molecules have high affinity towards bacterial Enoyl-ACP reductase. Docking predicts binding affinity value of -6.6kcal/mol for the ligand-ACP-recutase complex. The

computational predictions were complemented by the *in vitro* antibacterial activity evaluation.

5. Conclusion

We have reported complete structural and vibrational properties of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea by using IR and Raman spectra and theoretical method (B3LYP/6-31G(d,p) (6D, 7F)). The calculated vibrational wave numbers of the fundamental modes showed good correlations with the experimental data. The stability of the molecule arising from hyper conjugative interactions and charge delocalization has been analyzed using NBO analysis. MEP predicts that the NH group and the nitrogen atom N₄, sulphur atom S₂₃ are the most reactive sites for nucleophilic and electrophilic attack, respectively. Local reactivity properties upon ALIE surfaces indicate that sulfur atoms could be prone to electrophilic attacks. Fukui f^+ function recognize carbon atoms of benzene ring and the area in near vicinity of sulfur atom as possible reaction centers, because electron density is gained there as a consequence of nucleophilic attack. On the other side Fukui f^- function recognizes the area between benzene ring and nitrogen atom as possible reaction center, since HIPPT molecule loses there electron density when it is under electrophilic attack. Investigation of BDE leads to the conclusions that HIPPT molecule is stable in open air and in the presence of oxygen. On the other side BDE values indicate that degradation could start by breaking the bond between C19–N20, because BDE value in this case is the lowest. RDF functions indicate that five atoms are having significant interactions with water molecules and those include atoms N2, N4, C5, H22 and S23. RDF of H22 has the shortest peak distance, nitrogen atom N4 has two distinct solvation spheres, while nitrogen atom N2 has the highest $g(r)$ value. Reorganization energies of holes and electrons of HIPPT molecule are better than thiourea molecule and eventually lead to the improved values of charge hopping rates, but it was shown that orbital overlap is better between thiourea molecules. k_{ET}^+ of HIPPT molecule is 80% higher than k_{ET}^+ of thiourea molecule. The molecular docking studies predict that the molecules have high affinity towards bacterial Enoyl-ACP reductase; a binding affinity value of -6.6kcal/mol for the ligand-ACP-recutase complexe and the computational predictions were complemented by the *in vitro* antibacterial activity evaluation.

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Figure captions

Fig.1 Optimized geometry of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea

Fig.2 Representative ALIE surface of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea

Fig. 3 Two different views, (a) and (b) of Fukui functions

Fig.4 BDE of all single acyclic bonds of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea molecule

Fig.5 RDFs of atoms with significant interactions with water

Fig.6**(a)** Superimposition of docked conformation (pink) over the co-crystallized conformation (yellow) of triclosan shows RMSD value close to zero, confirming the reliability of docking protocol. **(b)** The docked ligand (pink) binds at the same site where co-crystallized triclosan (yellow) binds.

Table1

Optimized geometrical parameters of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea

Bond lengths (Å)

N1-C9	1.4568	N1-C19	1.3559	N1-H24	1.0118
N2-C3	1.3689	N2-C6	1.3821	N2-C7	1.4567
C3-N4	1.3158	C3-H10	1.0823	N4-C5	1.3770
C5-C6	1.3729	C5-H11	1.0812	C6-H12	1.0795
C7-C8	1.5339	C7-H13	1.0957	C7-H14	1.0954
C8-C9	1.5349	C8-H15	1.0967	C8-H16	1.0941
C9-H17	1.0929	C9-H18	1.0966	C19-N20	1.3746
C19-S23	1.6869	N20-C21	1.4168	N20-H22	1.0106
C21-C25	1.4041	C21-C26	1.4029	C25-C29	1.3954
C25-H34	1.0847	C26-C27	1.3927	C26-H30	1.0862
C27-C28	1.3966	C27-H31	1.0858	C28-C29	1.3949
C28-H32	1.0853	C29-H33	1.0860		

Bond angles (°)

C9-N1-C19	124.0	C9-N1-H24	117.1	C19-N1-H24	117.4
C3-N2-C6	106.3	C3-N2-C7	126.8	C6-N2-C7	126.9
N2-C3-N4	112.5	N2-C3-H10	121.6	N4-C3-H10	125.9
C3-N4-C5	104.9	N4-C5-C6	110.8	N4-C5-H11	121.4
C6-C5-H11	127.8	N2-C6-C5	105.6	N2-C6-H12	121.8
C5-C6-H12	132.6	N2-C7-C8	113.0	N2-C7-H13	108.6
N2-C7-H14	107.2	C8-C7-H13	110.1	C8-C7-H14	110.6
H13-C7-H14	107.0	C7-C8-C9	111.5	C7-C8-H15	109.3
C7-C8-H16	109.6	C9-C8-H15	110.3	C9-C8-H16	108.5
H15-C8-H16	107.6	N1-C9-C8	113.2	N1-C9-H17	107.3
N1-C9-H18	107.4	C8-C9-H17	110.1	C8-C9-H18	110.6
N17-C9-H18	108.1	N1-C19-N20	116.4	N1-C19-S23	124.2
N20-C19-S23	119.4	C19-N20-C21	130.0	C19-N20-H22	112.4
C21-N20-H22	117.4	N20-C21-C25	122.1	N20-C21-C26	118.5
C25-C21-C26	119.3	C21-C25-C29	119.9	C21-C25-H34	119.9
C29-C25-H34	120.2	C21-C26-C27	120.2	C21-C26-H30	119.3
C27-C26-H30	120.4	C26-C27-C28	120.4	C26-C27-H31	119.4

C28-C27-H31	120.1	C27-C28-C29	119.4	C27-C28-H32	120.3
C29-C28-H32	120.3	C25-C29-C28	120.6	C25-C29-H33	119.2
C28-C29-H33	120.1				
<u>Dihedral angles (°)</u>					
C19-N1-C9-C8	-84.9	C19-N1-C9-H17	36.8	C19-N1-C9-H18	152.8
H24-N1-C9-C8	81.1	H24-N1-C9-H17	-157.2	H24-N1-C9-H18	-41.2
C9-N1-C19-N20	176.7	C9-N1-C19-S23	-3.0	H24-N1-C19-N20	10.7
H24-N1-C19-S23	-169.0	C6-N2-C3-N4	0.3	C6-N2-C3-H10	179.8
C7-N2-C3-N4	177.5	C7-N2-C3-H10	-3.0	C3-N2-C6-C5	-0.3
C3-N2-C6-H12	-179.9	C7-N2-C6-C5	-177.4	C7-N2-C6-H12	2.9
C3-N2-C7-C8	-103.1	C3-N2-C7-H13	134.4	C3-N2-C7-H14	19.0
C6-N2-C7-C8	73.5	C6-N2-C7-H13	-49.0	C6-N2-C7-H14	-164.3
N2-C3-N4-C5	-0.2	H10-C3-N4-C5	-179.7	C3-N4-C5-C6	0.0
C3-N4-C5-H11	179.6	N4-C5-C6-N2	0.1	N4-C5-C6-H12	179.7
H11-C5-C6-N2	-179.4	H11-C5-C6-H12	0.2	N2-C7-C8-C9	178.9
N2-C7-C8-H15	56.7	N2-C7-C8-H16	-60.9	H13-C7-C8-C9	-59.5
H13-C7-C8-H15	178.4	H13-C7-C8-H16	60.7	H14-C7-C8-C9	58.6
H14-C7-C8-H15	-63.5	H14-C7-C8-H16	178.8	C7-C8-C9-N1	176.6
C7-C8-C9-H17	56.6	C7-C8-C9-H18	-62.8	H15-C8-C9-N1	-61.8
H15-C8-C9-H17	178.2	H15-C8-C9-H18	58.7	H16-C8-C9-N1	55.8
H16-C8-C9-H17	-64.3	H16-C8-C9-H18	176.3	N1-C19-N20-C21	3.7
N1-C19-N20-H22	-170.7	S23-C19-N20-C21	-176.5	S23-C19-N20-H22	9.0
C19-N20-C21-C25	45.3	C19-N20-C21-C26	-137.6	H22-N20-C21-C25	-140.5
H22-N20-C21-C26	36.7	N20-C21-C25-C29	178.7	N20-C21-C25-H34	0.8
C26-C21-C25-C29	1.6	C26-C21-C25-H34	-176.3	N20-C21-C26-C27	-177.6
N20-C21-C26-H30	2.8	C25-C21-C26-C27	-0.4	C25-C21-C26-H30	-180.0
C21-C25-C29-C28	-1.4	C21-C25-C29-H33	-180.0	H34-C25-C29-C28	176.4
H34-C25-C29-H33	-2.2	C21-C26-C27-C28	-0.9	C21-C26-C27-H31	179.8
H30-C26-C27-C28	178.6	H30-C26-C27-H31	-0.6	C26-C27-C28-C29	1.1
C26-C27-C28-H32	-179.4	H31-C27-C28-C29	-179.6	H31-C27-C28-H32	-0.1
C27-C28-C29-C25	0.0	C27-C28-C29-H33	178.6	H32-C28-C29-C25	-179.5
<u>H32-C28-C29-H33</u>	<u>-0.9</u>				

Table 2

Calculated scaled wave numbers, observed IR, Raman bands and assignments of HIPPT

B3LYP/6-31G(d,p) (6D, 7F) IR			Raman		Assignments ^a
$\nu(\text{cm}^{-1})$	IR_I	R_A	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3486	51.17	107.18	-	-	$\nu\text{NH}(99)$
3453	44.77	104.11	3448	-	$\nu\text{NH}(99)$
3156	2.01	80.79	3160	3152	$\nu\text{CHR}(98)$
3128	6.60	108.04	-	-	$\nu\text{CHR}(97)$
3121	4.53	49.64	3118	3119	$\nu\text{CHR}(97)$
3092	5.82	251.91	-	3094	$\nu\text{CHPh}(98)$
3086	17.08	78.20	-	-	$\nu\text{CHPh}(94)$
3077	15.18	87.71	-	3077	$\nu\text{CHPh}(98)$
3067	1.34	120.09	-	3055	$\nu\text{CHPh}(94)$
3062	4.70	16.50	-	-	$\nu\text{CHPh}(97)$
3006	13.31	14.71	3003	3007	$\nu\text{CH}_2(94)$
2993	5.11	10.44	-	2993	$\nu\text{CH}_2(91)$
2973	5.14	56.01	-	2970	$\nu\text{CH}_2(98)$
2940	49.42	26.69	2951	2945	$\nu\text{CH}_2(91)$
2931	16.90	169.29	-	2932	$\nu\text{CH}_2(95)$
2930	14.63	27.31	2928	-	$\nu\text{CH}_2(94)$
1593	36.91	162.63	1596	1588	$\nu\text{Ph}(63), \delta\text{CHPh}(11)$
1577	14.12	4.16	1577	-	$\nu\text{Ph}(68), \delta\text{NH}(12)$
1514	403.77	13.13	1517	1522	$\delta\text{NH}(48), \nu\text{CNR}(20)$
1496	26.64	2.22	-	-	$\nu\text{C}=\text{C}(44), \nu\text{CNR}(20), \delta\text{CHR}(25)$
1486	339.19	43.04	1490	-	$\delta\text{NH}(39), \nu\text{CN}(17), \delta\text{CHPh}(12)$
1484	59.21	9.91	-	1482	$\nu\text{C}=\text{C}(17), \delta\text{CHR}(26), \nu\text{CNR}(38)$
1475	4.05	0.30	-	-	$\delta\text{CHPh}(24), \delta\text{NH}(15), \nu\text{Ph}(48)$
1457	3.56	4.12	1458	-	$\delta\text{CH}_2(84)$
1440	14.74	33.53	1444	1444	$\delta\text{CH}_2(49), \nu\text{Ph}(42)$
1439	21.22	6.20	-	-	$\delta\text{CH}_2(66)$
1419	43.04	23.87	1417	-	$\delta\text{CH}_2(58)$
1378	8.48	11.56	-	1382	$\delta\text{CH}_2(64)$
1372	6.25	7.40	-	-	$\nu\text{CNR}(41), \delta\text{CH}_2(33)$
1357	51.96	13.18	1360	-	$\delta\text{CH}_2(61), \nu\text{CN}(10)$

1344	7.23	16.33	-	1350	ν CNR(52), ν C=C(14)
1325	118.90	6.29	1329	1324	ν CN(46), δ CH ₂ (10), δ CHPh(27)
1305	21.64	5.83	1310	-	ν Ph(70)
1302	101.84	22.53	-	-	δ CH ₂ (67)
1287	80.75	22.43	-	-	δ CH ₂ (18), δ CHPh(51), ν CN(19)
1271	10.18	15.61	-	-	δ CH ₂ (37), δ CHR(36), ν CNR(10)
1261	15.49	7.91	1260	1263	δ CHR(30), δ CH ₂ (23)
1244	11.63	6.11	-	1239	δ CH ₂ (80)
1220	43.62	6.16	-	-	δ CHR(40), ν CN(33)
1213	103.36	34.28	1215	-	δ NH(16), ν CN(45), ν Ph(11)
1198	35.77	19.04	1195	-	ν CN(19), δ CH ₂ (27)
1159	4.00	11.28	1162	1165	δ CHPh(76), ν Ph(11)
1143	0.42	7.25	-	-	δ CHPh(80), ν Ph(13)
1141	34.44	9.22	-	-	ν CN(48), δ CH ₂ (23)
1105	13.22	6.18	1101	1108	ν CNR(48), δ CHR(29)
1098	20.55	2.52	1094	-	ν CN(22), δ CH ₂ (21), ν CNR(12)
1068	7.88	1.40	1071	1072	ν Ph(43), δ CHPh(33)
1058	28.95	10.85	-	-	δ CHR(57), ν C=C(17)
1044	38.05	2.00	1047	-	δ CH ₂ (53), ν CN(13)
1022	12.33	18.58	1022	-	ν CC(63), δ CH ₂ (32)
1014	0.74	15.62	1016	1014	ν Ph(57), δ CHPh(23)
1007	13.38	5.70	1004	-	δ R(35), ν CN(39), ν CC(11)
987	9.25	4.21	984	-	ν CC(79)
976	0.71	51.40	-	-	δ Ph(67), ν Ph(17)
960	0.32	0.49	955	-	γ CHPh(84), τ Ph(13)
937	0.23	0.77	935	-	γ CHPh(84)
889	2.93	2.22	890	902	γ CHPh(80)
880	12.59	3.11	-	-	ν CS(64)
835	3.01	5.07	836	839	δ CH ₂ (64)
825	2.14	1.76	-	-	γ CHR(81)
824	2.49	6.13	-	-	γ CHPh(56), γ CH ₂ (12)
825	0.74	4.19	811	-	γ CHPh(49), δ Ph(15), ν Ph(14)
784	6.52	3.91	-	-	δ NH(25), γ CN(20), ν CN(22)
772	25.31	0.69	-	-	γ CHR(80), τ R(13)

734	35.08	2.12	733	-	γ CHPh(57), τ Ph(14)
725	8.73	3.22	-	-	δ CH ₂ (66)
701	3.19	3.47	703	703	δ R(36), ν CN(15)
700	20.72	1.48	703	-	γ CHR(91)
682	10.93	1.51	684	-	τ Ph(68), γ CHPh(18)
649	13.10	0.29	648	644	τ R(93)
613	1.29	3.04	615	-	τ R(61)
610	8.56	5.08	-	-	δ Ph(29), τ R(26), γ CS(15)
605	11.37	1.16	-	605	γ CS(47), δ Ph(31)
597	12.05	4.95	595	585	δ Ph(28), γ CS(18), ν CS(11)
563	3.85	6.05	-	-	δ NH(27), δ CS(38), δ Ph(17)
510	91.57	20.17	511	508	τ CS(38), γ NH(26), τ NH(22)
490	7.66	3.58	492	491	τ Ph(42), γ CN(30)
478	98.59	4.03	474	-	τ NH(33), γ NH(27), τ CH ₂ (15)
452	14.27	3.18	448	448	δ CH ₂ (50), τ Ph(22)
402	5.29	4.50	403	398	τ Ph(79)
366	4.85	1.04	-	-	δ CN(32), δ CH ₂ (10), τ Ph(23)
326	0.29	0.73	-	-	δ CN(71)
301	2.06	5.65	-	-	τ Ph(22), δ CN(28), δ NH(13)
284	2.20	5.29	-	288	δ CS(33), δ NH(21)
256	4.60	1.23	-	-	δ CS(26), δ NH(27)
238	2.15	0.62	-	-	δ CH ₂ (52), γ CN(17)
197	2.15	2.44	-	192	τ Ph(29), δ CN(10), δ CH ₂ (14)
122	1.54	1.66	-	-	τ CH ₂ (57), τ Ph(13), δ CN(15)
112	2.40	4.19	-	-	γ CN(18), τ NH(21), γ NH(16)
91	0.55	3.37	-	-	γ CN(32), δ NH(28)
69	2.26	1.40	-	-	τ CS(11), γ NH(16), τ CH ₂ (24), τ NH(11)
57	2.75	3.42	-	-	γ NH(22), τ CS(21), τ CH ₂ (15), γ CN(15)
45	3.91	5.08	-	-	τ NH(50), δ NH(15)
26	1.41	5.17	-	-	τ NH(29), τ CH ₂ (28)
23	1.63	7.34	-	-	τ CN(40), τ NH(16), τ CH ₂ (22)
15	0.90	7.42	-	-	τ CS(22), τ NH(22), τ CH ₂ (21), γ NH(11)

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; phenyl ring and imidazole ring are designated as Ph and R.

Table 3

The predicted ^1H and ^{13}C NMR isotropic chemical shifts (with respect to TMS, all values are in ppm)

Atom	σ_{TMS}	B3LYP/6-31G(d,p)(6D, 7F) σ_{calc}	$\delta_{\text{calc}}(\sigma_{\text{TMS}} - \sigma_{\text{calc}})$
C3	196.852	62.9129	133.9391
C5	196.852	65.9339	130.9181
C6	196.852	79.1076	117.7444
C7	196.852	146.4285	50.4235
C8	196.852	157.8485	39.0035
C9	196.852	148.5631	48.2889
C19	196.852	16.4963	180.3557
C21	196.852	60.1938	136.6582
C25	196.852	75.9626	120.8894
C26	196.852	74.7762	122.0758
C27	196.852	66.1715	130.6805
C28	196.852	72.1923	124.6597
C29	196.852	67.4748	129.3772
H10	32.7711	24.6798	8.0913
H11	32.7711	24.6676	8.1035
H12	32.7711	24.8438	7.9273
H13	32.7711	27.9497	4.8214
H14	32.7711	28.358	4.4131
H15	32.7711	30.6343	2.1368
H16	32.7711	29.094	3.6771
H17	32.7711	27.5088	5.2623
H18	32.7711	29.0296	3.7415
H22	32.7711	24.827	7.9441
H24	32.7711	26.1167	6.6544
H30	32.7711	24.8903	7.8808
H31	32.7711	24.282	8.4891
H32	32.7711	24.555	8.2161
H33	32.7711	24.3395	8.4316
H34	32.7711	25.5467	7.2244

Table 4

Second-order perturbation theory analysis of Fock matrix in NBO basis corresponding to the intramolecular bonds of the title compound.

Donor(i)	Type	ED/e	Acceptor(j)	Type	ED/e	E(2) ^a	E(j)-E(i) ^b	F(i,j) ^c
N1-C19	σ	1.98918	N1-C19	σ^*	0.05632	1.35	1.20	0.036
N2-C3	σ	1.98644	N2-C6	σ^*	0.02239	2.02	1.26	0.045
-	-	-	N2-C7	σ^*	0.02688	3.39	1.15	0.056
C5-C6	σ	1.98566	N2-C7	σ^*	0.02688	5.22	1.04	0.066
C5-C6	π	1.86103	C3-N4	π^*	0.38317	14.98	0.28	0.061
C7-C8	σ	1.97961	N1-C9	σ^*	0.01652	2.57	0.96	0.044
-	-	-	N2-C3	σ^*	0.04194	1.06	1.09	0.031
C8-C9	σ	1.98089	N2-C7	σ^*	0.02688	2.61	0.96	0.045
C19-N20	σ	1.98697	N1-C9	σ^*	0.01652	2.98	1.19	0.053
-	-	-	N20-C21	σ^*	0.03552	1.89	1.25	0.044
-	-	-	C21-C26	σ^*	0.02372	1.06	1.39	0.034
C21-C25	σ	1.97517	N20-C21	σ^*	0.02372	3.71	1.26	0.061
-	-	-	C25-C29	σ^*	0.01464	2.58	1.28	0.051
-	π	1.66375	C26-C27	π^*	0.32349	18.19	0.29	0.065
-	-	-	C28-C29	π^*	0.33009	20.55	0.29	0.069
C21-C26	σ	1.97494	C19-N20	σ^*	0.03552	1.10	1.12	0.031
-	-	-	C21-C25	σ^*	0.02587	3.73	1.25	0.061
-	-	-	C26-C27	σ^*	0.01411	2.48	1.28	0.050
LPN1	σ	1.69665	C8-C9	σ^*	0.02177	7.27	0.64	0.066
LPN2	σ	1.55493	C3-N4	π^*	0.38317	47.41	0.27	0.103
-	-	-	C5-C6	π^*	0.30631	31.35	0.29	0.088
-	-	-	C7-C8	σ^*	0.01960	6.16	0.61	0.062
LPN4	σ	1.55493	N2-C3	σ^*	0.04194	9.26	0.82	0.078
-	-	-	C5-C6	σ^*	0.01855	5.58	0.95	0.066
LPN20	σ	1.68773	C21-C25	σ^*	0.02587	2.94	0.81	0.047
-	-	-	C21-C25	π^*	0.39609	20.99	0.27	0.069
-	-	-	C21-C26	σ^*	0.02372	2.84	0.81	0.046
LPS23	σ	1.98651	N1-C19	σ^*	0.05632	3.00	1.15	0.053

-	-	-	C19-N20	σ^*	0.05473	2.38	1.13	0.047
-	π	1.88315	N1-C19	σ^*	0.05632	10.70	0.65	0.076
-	-	-	C19-N20	σ^*	0.05473	9.73	0.63	0.071

^aE(2) means energy of hyper-conjugative interactions (stabilization energy in kJ/mol)

^bEnergy difference (a.u) between donor and acceptor i and j NBO orbitals

^cF(i,j) is the Fock matrix elements (a.u) between i and j NBO orbitals

Table 5

NBO results showing the formation of Lewis and non-Lewis orbitals.

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ N1-C19	1.98918	61.32	38.68	0.7830(sp ^{1.70})N	37.09	62.91
-	-0.86023	-	-	+0.6220(sp ^{2.14})C	31.76	68.24
σ N2-C3	1.98644	64.51	35.49	0.8032(sp ^{1.99})N	33.39	66.61
-	-0.79584	-	-	+0.5958(sp ^{2.32})C	30.12	69.88
σ C5-C6	1.98566	48.66	51.34	0.6975(sp ^{1.73})C	36.59	63.41
-	-0.69086	-	-	+0.7165(sp ^{1.63})C	37.95	62.05
π C5-C6	1.86103	48.51	51.49	0.6965(sp ^{1.00})C	0.00	100.0
-	-0.24858	-	-	+7175(sp ^{1.00})C	0.00	100.0
σ C7-C8	1.97961	50.49	49.51	0.7106(sp ^{2.47})C	28.83	71.17
-	-0.61546	-	-	+0.7036(sp ^{2.78})C	26.14	73.86
σ C8-C9	1.98089	49.89	50.11	0.7063(sp ^{2.78})C	26.42	73.58
-	-0.61291	-	-	+0.7079(sp ^{2.49})C	28.67	71.33
σ C19-N20	1.98697	38.34	61.66	0.6192(sp ^{2.25})C	30.78	69.22
-	-0.84579	-	-	+0.7852(sp ^{1.72})N	36.73	63.27
σ C21-C25	1.97517	50.93	49.07	0.7136(sp ^{1.74})C	36.47	63.52
-	-0.71706	-	-	+0.7005(sp ^{1.92})C	34.19	65.81
π C21-C25	1.66375	49.41	50.59	0.7029(sp ^{99.99})C	0.02	99.98
-	-0.27255	-	-	+0.7113(sp ^{99.99})C	0.03	99.97
σ C21-C26	1.97494	51.12	48.88	0.7150(sp ^{1.76})C	36.16	63.84
-	-0.71391	-	-	+0.6992(sp ^{1.90})C	34.43	65.57
n1N1	1.69665	-	-	sp ^{84.31}	1.17	98.83
-	-0.27148	-	-	-	-	-
n1N2	1.55493	-	-	sp ^{99.99}	0.04	99.96
-	-0.24756	-	-	-	-	-
n1N4	1.92764	-	-	sp ^{1.97}	33.61	66.39
-	-0.34090	-	-	-	-	-
n1N20	1.68773	-	-	sp ^{99.99}	0.10	99.90
-	-0.26693	-	-	-	-	-
n1S23	1.98651	-	-	sp ^{0.21}	82.50	17.50
-	-0.68928	-	-	-	-	-

n2S23	1.88315	-	-	sp ^{99.99}	0.01	99.99
-	-0.19117	-	-	-	-	-
n3S23	1.59478	-	-	sp ^{1.00}	0.00	100.0
-	-0.18631	-	-	-	-	-

^a ED/e is expressed in a.u.

Table 6. Reorganization energies, charge coupling and charge transfer rates of thiourea and HIPPT molecules

Structure	λ_- [eV]	λ_+ [eV]	t [eV]	k_{ET}^- [s ⁻¹]	k_{ET}^+ [s ⁻¹]
Thiourea	0.80	0.33	0.15	2.92×10^{11}	2.01×10^{13}
HIPPT	0.67	0.21	0.08	2.96×10^{11}	3.65×10^{13}

Table 7

Zones of inhibition (mm) $\pm$ SD* obtained with title compound and standard drugs against multiple bacterial strains.

Compound	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
HIPPT	14 $\pm$ 1.4	26 $\pm$ 1.6	13 $\pm$ 1.3	20 $\pm$ 1.2
Streptomycin	19 $\pm$ 1.2	25 $\pm$ 1.6	22 $\pm$ 1.8	25 $\pm$ 1.8
Ciprofloxacin	15 $\pm$ 1.8	20 $\pm$ 2.0	26 $\pm$ 1.4	22 $\pm$ 1.6

*The experiments were done in triplicate and standard deviation as observed is reported with the inhibition value.

Fig.1 Optimized geometry of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea

157.05 ALIE [kcal/mol] 352.57

Fig.2 Representative ALIE surface of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea

Fig.3 Two different views, (a) and (b) of Fukui functions

Fig.4 BDE of all single acyclic bonds of 1-[3-(1H-imidazol-1-yl)propyl]-3-phenylthiourea molecule

Fig.5 RDFs of atoms with significant interactions with water

Fig.6 (a) Superimposition of docked conformation (pink) over the co-crystallized conformation (yellow) of triclosan shows RMSD value close to zero, confirming the reliability of docking protocol. (b) The docked ligand (pink) binds at the same site where co-crystallized triclosan (yellow) binds.

Scheme -synthetic pathway of the title compound

Highlights

- The geometrical parameters were optimized by DFT method
- Title compound has been characterized by IR and Raman spectroscopy
- NLO parameters are calculated and the computed hyperpolarizability is very large
- NBO analysis is carried out to study hyper conjugative interactions
- Investigated compound is highly effective against both gram positive and gram negative bacteria