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FT-IR, NBO, HOMO-LUMO, MEP analysis and molecular docking study of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino)[(methoxycarbonyl)imino]methylcarbamate

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Abstract

The optimized molecular structure, vibrational frequencies, corresponding vibrational assignments of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl) phenyl]amino)[(methoxycarbonyl)imino]methylcarbamate have been investigated using HF and DFT levels of calculations. The geometrical parameters are in agreement with XRD data. The stability of the molecule arising from hyper-conjugative interaction and charge delocalization has been analyzed using NBO analysis. The HOMO and LUMO analysis is used to determine the charge transfer within the molecule. Molecular electrostatic potential study was also performed. The first and second hyperpolarizability was calculated in order to find its role in nonlinear optics. Molecular docking studies are also reported. Prediction of Activity Spectra analysis of the title compound predicts

antihelmintic and antiparasitic activity as the most probable activity with Pa (probability to be active) value of 0.808 and 0.797 respectively. Molecular docking studies show that both the phenyl groups and the carbonyl oxygens of the molecule are crucial for bonding and these results draw us to the conclusion that the compound might exhibit pteridine reductase inhibitory activity.

Keywords: DFT; molecular docking; FT-IR; methoxy; hyperpolarizability.

1. Introduction

Febantel, N-{2-[2,3-bis(methoxycarbonyl)-guanido]-5-(phenylthio)-phenyl}-2-methoxy acetamide is used as anthelmintic against gastrointestinal parasites in animals [1,2]. It is a pro-drug, which gets converted into an active compound soon after administration [3]. The metabolite pathway of febantel is converted directly to either fenbendazole or oxfendazole, which is achieved via febantel sulfoxide as an intermediate. Sulfenyl carbonyl compounds are an interesting family of molecules related to important biological systems and the anomeric and mesomeric effects in methoxycarbonyl sulfenyl chloride is reported by Erben et al. [4]. Vallejos et al. [5] reported the experimental investigation of the structure and vibrational properties of methoxycarbonylsulfenyl isocyanate. Raj et al. [6] reported the IR, Raman, surface enhanced Raman scattering and computational study of a benzylsulfonyl derivative. Fun et al. [7] reported the single crystal XRD study of the title compound. In the present study, IR spectrum of the title compound has been reported both experimentally and theoretically. The energies, degrees of hybridization, population of the lone pairs of oxygen, nitrogen atoms, energies of their interaction with the anti-bonding of the rings and the electron density distributions and stabilization energies have been calculated by natural bonding orbital analysis using density functional theory method to give clear evidence of stabilization originating from the hyper-conjugation of various intra-molecular interactions. There has been growing interest in using organic materials for nonlinear optical devices because of the large second order electric susceptibilities and since the second order electric susceptibility is related to first hyperpolarizability, the search for organic chromophores with large first hyperpolarizability is fully justified. Due to the different potential biological activities of the title compound, molecular docking of the title compound is also reported.

2. Experimental

A febantel sample was obtained from CAD Pharma Ltd., Bangalore. Crystal of the title compound was obtained from ethanol by slow evaporation method. FT-IR spectrum (Fig.1) was recorded using KBr pellets on a Shimadzu-FTIR infrared spectrometer.

3. Computational section

Calculations of the title compound are carried out with Gaussian09 software package [8] using the HF/6-31G(d) (6D, 7F), B3LYP/6-31G(d) (6D, 7F) and B3LYP/6-311++G(d,p) (5D, 7F) basis sets to predict the molecular structure and vibrational wave numbers. Molecular geometry was fully optimized by Berny's optimization algorithm using redundant internal coordinates. Harmonic vibrational wave numbers are calculated using the analytic second derivatives to confirm the convergence to minima on the potential surface. The wave number values computed at the Hartree-Fock level contain known systematic errors due to the negligence of electron correlation [9]. We therefore, have used the scaling factor value of 0.8929 for HF method [9]. The DFT hybrid B3LYP functional tends to overestimate the fundamental modes; therefore scaling factor of 0.9613 has to be used for obtaining a considerably better agreement with experimental data [9]. Parameters corresponding to optimized geometry of the title compound (Fig.2) with XRD data are given in Table 1. The absence of imaginary wave numbers on the calculated vibrational spectrum confirms that the structure deduced corresponds to minimum energy. The assignments of the calculated wave numbers are aided by the animation option of Gaussview program, which gives a visual presentation of the vibrational modes [10]. The potential energy distribution (PED) is calculated with the help of GAR2PED software [11].

4. Results and discussion

4.1. Geometrical parameters

The C-C bond lengths in the phenyl rings are in the range, 1.3989-1.4013Å (DFT), 1.3830-1.3989Å (XRD) for PhI and 1.3927-1.4155Å (DFT), 1.3868-1.4036Å (XRD) for PhII. Both benzene rings are regular hexagons with bond lengths somewhere in between the normal values for a single (1.54Å) and a double (1.33Å) bond [12]. The C-N bond lengths are in the range 1.3521-1.4337 (DFT) and 1.3410-1.4288 (XRD) and these values show an excellent agreement between the theoretical and experimental

results of the title compound. The bond lengths, C₂₁-N₁₀ (1.3245/1.3241) is significantly longer than a C=N double bond (1.22Å) [13], suggesting that some multiple bond character is present. In the present case, the C=O bond lengths are 1.2492, 1.2655, 1.2513Å (DFT), 1.2081, 1.2289, 1.2296Å (XRD) and Lukose *et al.* [14] reported the C=O bond length as 1.2486Å. For the title compound, the C-O bond lengths lie in the range 1.3634-1.4722 (DFT), 1.3357-1.4502Å (XRD) and in agreement with the reported values [12]. In the title compound, the C-S bond lengths lie in the range 1.8530-1.8549 (DFT) and 1.7712-1.7720Å (XRD), while the reported values are in the range 1.7675-1.8641 [12] and 1.771-1.7846, 1.783-1.811Å [16]. The asymmetry of bond angles at C₃₂, C₂₇ and C₂₂ positions reveal hydrogen bondings in the crystal network [7].

4.2. IR spectrum

The calculated (scaled) wavenumbers, observed IR bands and assignments are given in Table 2. In the following discussion, the mono substituted and tri substituted phenyl rings are designated as PhI and PhII, respectively. Since the frequencies given by B3LYP/6-311++G(d,p) (5D, 7F) calculations are in agreement with observed values, these theoretical values are compared with IR bands.

For the title compound, the C-S stretching modes [15] appear at 685 cm⁻¹ in the IR spectrum and the theoretically calculated values are 685 and 677 cm⁻¹. The C-S stretching mode is reported at about 641 cm⁻¹ (IR) and 704, 640 (DFT) by Mary et al. [16] and at 658 (IR) and at 663, 704 cm⁻¹ theoretically [17] for sulfanyl derivatives.

The stretching mode of NH group is generally give rise to bands [15, 18] in the range 3500–3300 cm⁻¹. For the title compound, the NH stretching mode are observed at 3415, 3366, 3231 cm⁻¹ in the IR spectrum and theoretically at 3333, 3326, 3211 cm⁻¹ (DFT). The NH stretching wave number is red shifted by 82 cm⁻¹ in IR from the computed wave number, which indicates the weakening of the NH bond as reported in literature [7, 19]. The NH deformation mode is expected in the range 1500-1625 cm⁻¹ [20] and in the present case the band observed at 1673, 1600⁻¹ in IR and 1696, 1679, 1602 cm⁻¹ (DFT) is assigned as the NH deformation mode. The out-of-plane NH wagging modes are assigned at 926, 822, 774 cm⁻¹ theoretically. Aromatic compounds with nitrogen directly attached to the ring absorb at 1330-1260 cm⁻¹ because of the stretching of the phenyl C-N bond [20]. For the title compound, the C-N stretching modes are

observed at 1332 cm^{-1} in the IR spectrum and at $1334, 1252\text{ cm}^{-1}$ theoretically. The other C-N stretching modes are assigned at $1210, 1203, 1197, 1055\text{ cm}^{-1}$ theoretically. The C-N stretching band is reported in the range $1000\text{-}1200\text{ cm}^{-1}$ [21].

According to literature [22] the stretching mode of C=O is expected in the range $1850\text{-}1550\text{ cm}^{-1}$. The in-plane bending mode of C=O is reported in the range $725 \pm 95\text{ cm}^{-1}$ [15]. The C=O out of plane vibration is reported in the region $595 \pm 120\text{ cm}^{-1}$ [15]. Kumar et al. reported the C=O stretching modes 2-(4-chlorophenyl)-2-oxoethy-3-nitrobenzoate at $1728, 1703\text{ cm}^{-1}$ in the IR spectrum and the theoretical values are $1739, 1720\text{ cm}^{-1}$ [23]. For the title compound, the bands $1624, 1600, 1540\text{ cm}^{-1}$ in IR spectrum and at $1618, 1602, 1532$ (DFT) are assigned as the C=O stretching modes. The deformation modes of C=O are assigned at $735, 665, 642, 520\text{ cm}^{-1}$ in the IR spectrum and at $732, 697, 649, 662, 522\text{ cm}^{-1}$ theoretically. The C-O-C stretching vibrations are expected in the regions $1200\text{-}1100\text{ cm}^{-1}$ (asymmetric) and $1050\text{-}950\text{ cm}^{-1}$ (symmetric) [15, 24]. The skeletal deformation modes of C-O-C can be found in the region $320 \pm 50\text{ cm}^{-1}$ [15]. As expected the asymmetric C-O-C vibrations is assigned at $1222, 1164, 1149\text{ cm}^{-1}$ in the IR spectrum with DFT values at $1220, 1164, 1154\text{ cm}^{-1}$ and the symmetric C-O-C stretching vibrations are assigned at $1104, 1046\text{ cm}^{-1}$ in IR and at $1096, 1053, 1044\text{ cm}^{-1}$ theoretically for the title compound [21]. The deformation modes of C-O-C are reported at $604, 606$ and 287 cm^{-1} experimentally [25]. Mary et al. reported the C-O-C stretching modes at $1101, 1099$ (experimentally) and at $1102, 942, 940\text{ cm}^{-1}$ theoretically for phenylprop-2-enoic anhydride derivatives [26, 27].

The vibrations of the CH_2 group, the asymmetric stretch $\nu_{\text{as}}\text{CH}_2$, symmetric stretch $\nu_{\text{s}}\text{CH}_2$, scissoring vibration δCH_2 , appear in the region $2945 \pm 45, 2885 \pm 45$ and $1445 \pm 35\text{ cm}^{-1}$, respectively [15, 20]. The DFT calculations give $\nu_{\text{as}}\text{CH}_2$ at 2908 cm^{-1} and $\nu_{\text{s}}\text{CH}_2$ at 2864 cm^{-1} . The bands observed at $2912, 2870\text{ cm}^{-1}$ (IR) are assigned as the stretching modes of CH_2 group. Bands of hydrocarbons due to CH_2 twisting and wagging vibrations are observed in the region $1180\text{-}1390\text{ cm}^{-1}$ and rocking modes are expected in the range $850 \pm 35\text{ cm}^{-1}$ [20, 21]. In the present case, the band observed at $1188, 987\text{ cm}^{-1}$ in the IR and $1433, 1315, 1185, 985\text{ cm}^{-1}$ (theoretical) are assigned as the deformation modes of CH_2 groups. The stretching vibrations of the CH_3 group are expected in the range of $2900\text{-}3050\text{ cm}^{-1}$ [15, 20]. In the present case, the asymmetric

stretching modes of the methyl group are calculated to be in the range 2939-3060 cm^{-1} and the symmetric modes in the range 2871-2929 cm^{-1} . Experimentally these bands are observed at 2980, 2942 cm^{-1} in the IR spectrum. The asymmetric and symmetric bending vibrations of the methyl group normally appear in the region of 1400-1485 cm^{-1} and 1380-1420 cm^{-1} [15, 22]. The bands observed at 1458, 1399 cm^{-1} in the IR spectrum was assigned as CH_3 bending modes. The B3LYP calculations give these modes in the range 1398-1456 cm^{-1} . In the present case, the rocking modes of methyl group were calculated to be at 1136, 1129, 1127, 1112, 895, 891 cm^{-1} and were observed at 1118, 882 cm^{-1} in the IR spectrum. The torsion vibrations of the methyl groups were often assigned within the region $185 \pm 65 \text{ cm}^{-1}$ [15]. The C-C modes are also identified and assigned (Table 2).

Aromatic compounds commonly exhibit multiple weak bands in the region 3100-3000 cm^{-1} , due to aromatic CH stretching vibrations [15]. However, these bands are rarely useful because they overlap with one another resulting in stronger absorption in this region. The DFT calculations give the CH stretching modes of the phenyl rings in the range 3030-3071 for PhI and in the range 3050-3100 cm^{-1} for PhII. The bands observed at 3120, 3040 cm^{-1} in the IR spectrum was assigned as CH stretching modes of the phenyl rings. For the title compound, the bands at 1295, 1170, 1009 (IR), 1293, 1168, 1167, 1003 cm^{-1} (DFT) and 1090 (IR), 1253, 1129, 1094 (DFT) are assigned as the CH in-plane bending modes of the phenyl rings, PhI and PhII, respectively. The CH out-of-plane deformations are expected below 1000 cm^{-1} [15] and for the title compound, the DFT calculations give bands at 967, 965, 913, 810, 751 for PhI and 940, 859, 755 cm^{-1} for PhII as γCH modes. Experimentally bands are observed at 954, 912, 855, 811, 760 cm^{-1} in the IR spectrum.

The benzene ring possesses six ring stretching modes of which the four with the highest wavenumbers occurring near 1600, 1580, 1490 and 1440 cm^{-1} are good group vibrations [15]. The bands observed at 1565, 1449 cm^{-1} (IR), 1563, 1558, 1449, 1418, 1262 (DFT) and at 1565, 1550, 1447, 1374 (IR) and 1567, 1551, 1450, 1376, 1270 (DFT) are assigned as phenyl ring stretching modes of PhI and PhII rings, respectively. These modes are expected in the region 1250-1620 cm^{-1} [15]. The fifth ring stretching vibration is active near $1315 \pm 65 \text{ cm}^{-1}$, a region that overlaps strongly with that of the CH in-plane deformation. The sixth ring stretching vibration, or the ring breathing mode, appears as a

weak band near 1000 cm^{-1} in mono-, 1,3-di-, and 1,3,5-trisubstituted benzenes [15]. In the otherwise substituted benzenes, however, this vibration is substituent sensitive and difficult to distinguish from the ring in-plane deformation [15]. The ring breathing mode of the mono substituted benzene ring is assigned at 978 cm^{-1} in the IR spectrum and at 976 cm^{-1} theoretically as expected. In the case of tri-substituted benzenes, with mixed substituent, the ring breathing mode is expected in the range $600\text{--}750\text{ cm}^{-1}$ [28] and in the present case, the band observed at 744 cm^{-1} in the IR spectrum and at 742 cm^{-1} (DFT) is assigned as the ring breathing mode of the phenyl ring. Mary *et al.*, [29] reported the ring breathing mode of the tri-substituted benzene ring of 5-nitro-2-(p-fluorophenyl) benzoxazole at 738 cm^{-1} .

In order to investigate the performance of vibrational wave numbers of the title compound, the wave numbers are also calculated at HF/6-31G(d) (6D, 7F) and B3LYP/6-31G (6D, 7F) levels and the root mean square (RMS) value between the calculated and observed wave numbers were calculated. The RMS values of wave numbers were calculated using the following expression [30].

$$RMS = \sqrt{\frac{1}{n-1} \sum_i^n (v_i^{calc} - v_i^{exp})^2}$$

The RMS error of the observed IR bands are found to be 22.03 for HF/6-31G(d) (6D, 7F), 20.36 for B3LYP/6-31G(6D, 7F) and 7.29 for B3LYP/6-311++G(d,p)(5D, 7F) methods. The observed small differences between experimental and calculated vibrational modes are due to the fact that experimental results belong to solid phase and the theoretical calculations belong to gaseous phase.

4.3. Molecular Electrostatic Potential

Molecular electrostatic potential (MEP) surface demonstrates the distribution of charges across the surface of a molecule and the MEP plot is used to understand the reactive behavior of a molecule, in that the negative regions can be regarded as nucleophilic centers, whereas the positive regions are electrophilic sites [31, 32]. The electrostatic potential is also well suited for analyzing processes based on the “recognition” of one molecule by another, as in drug-receptor, an enzyme-substrate interactions, because it is through their potentials that the two species first “see” each

other [33, 34]. To predict reactive sites of electrophilic and nucleophilic attacks for the investigated molecule, MEP at the B3LYP/6-311++G(d,p)(5D, 7F) optimized geometry was calculated. The negative (red and yellow) regions of MEP were related to electrophilic reactivity and the positive (blue) regions to nucleophilic reactivity (Fig.3). The predominance of green region in the MEP surfaces corresponds to a potential halfway between the two extremes red and blue color. As can be seen from the MEP map of the title compound, negative regions are mainly localized over the carbonyl groups and the tri-substituted phenyl ring. The maximum positive regions are localized over the methyl groups and NH groups. As can be seen from the MEP map, regions having the negative potentials are over the electro negative atoms.

4.4. Nonlinear Optical properties (NLO)

Quantum chemical evaluation of the polarizability (α), and the first and second order hyperpolarizabilities (β and γ) is a field of intense research because it is related to the design of new compounds for nonlinear optical applications and to understand the interaction between electromagnetic field and matter [35, 36]. The hyperpolarizability and related properties have been calculated at DFT level by finite field approach [37], which is currently one of the methods for obtaining numerically accurate NLO responses. The components of first order hyperpolarizability are defined as the coefficients in the Taylor series expansion of energy in the external electric field. The total static dipole moment, mean polarizability and first and second order hyper polarizabilities can be deduced using the x, y and z components as:

$$\mu = \sqrt{(\mu_x^2 + \mu_y^2 + \mu_z^2)}$$

$$\alpha_o = \frac{\alpha_{xx} + \alpha_{yy} + \alpha_{zz}}{3}$$

The dipole moment μ , the mean polarizability α_o are calculated using Gaussian 09 software and is found to be 2.459 Debye and 4.349×10^{-23} esu., respectively. The first order hyper polarizability β was also calculated using the finite field approach theory. The components of first hyperpolarizability can be calculated using the following equation

$$\beta_i = \beta_{ijk} + \frac{1}{3} \sum (\beta_{ijj} + \beta_{jji} + \beta_{jji}), (i \neq j)$$

Using the x, y and z components, the magnitude of the first hyperpolarizability tensor can be calculated using

$$\beta_{total} = \sqrt{(\beta_x^2 + \beta_y^2 + \beta_z^2)}$$

The complete equation for calculating the magnitude of the first hyperpolarizability from Gaussian 09 output is as follows.

$$\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz}$$

$$\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yzz}$$

$$\beta_z = \beta_{zzz} + \beta_{xxz} + \beta_{yyz}$$

The first order hyperpolarizability of the title compound is calculated and is found to be 16.438×10^{-30} esu. The calculated hyperpolarizability of the title compound is 126.45 times that of the standard NLO material urea (0.13×10^{-30} esu) [38]. The average second hyperpolarizability is $\langle \gamma \rangle = (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz})/5$ [39-41]. The theoretical second order hyperpolarizability was calculated using the Gaussian09 software and is equal to -13.286×10^{-40} e.s.u. We conclude that the title compound and its derivatives are an attractive object for future studies of nonlinear optical properties.

4.5. Frontier molecular orbital analysis

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and their properties such as energy and energy gap are very useful data, since the energy of the HOMO is directly related to the ionization potential and LUMO is directly related to the electron affinity [42, 43]. The conjugated molecules are characterized by a small HOMO-LUMO separation, which is the result of a significant degree of intramolecular charge transfer from the end-capping electron-donor groups to the electron-acceptor group through a π -conjugated path [44]. The HOMO and LUMO plots are shown in Fig.4. In the title compound, the HOMO of π nature is delocalized over the phenyl rings and sulfur atom and in LUMO, only over the phenyl rings. The energy gap between HOMO and LUMO is a critical parameter to determine molecular electrical transport properties. By using HOMO and LUMO energy values for a molecule, the global chemical reactivity descriptors of molecules such as hardness(η), chemical potential(μ), electronegativity(χ) and electrophilicity index(ω) as well as local reactivity have been defined [45-49]. Pauling introduced the concept of electronegativity

as the power of an atom in a molecule to attract electrons to it. According to Koopman's theorem, $\eta = (I-A)/2 = 2.293$, $\mu = -(I+A)/2 = -5.935$, and $\chi = (I+A)/2 = 5.935$ where A and I are the ionization potential and electron affinity of the molecules. $I = -E_{\text{HOMO}} = 7.227$ eV and $A = -E_{\text{LUMO}} = 4.642$ eV. Electron affinity refers to the capability of a ligand to accept precisely one electron from a donor. Considering the chemical hardness, large HOMO-LUMO gap (2.585 eV) means a hard molecule and small gap means a soft molecule. One can also relate the stability of the molecule to hardness which means that the molecule with least energy gap means it is more reactive. Parr et al. [50] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω), which defines a quantitative classification of the global electrophilic nature of a molecule and $\omega = \mu^2/2\eta = 7.681$. The usefulness of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity [51-53].

4.6. Natural Bond Orbital analysis

The natural bond orbitals (NBO) calculations were performed using NBO 3.1 program [54] as implemented in the Gaussian09 package at the DFT/B3LYP level. The NBO analysis is a tool for understanding hydrogen bonding interactions and delocalization of electron density from occupied donor and unoccupied acceptor within the molecule. The second-order Fock-matrix was carried out to evaluate the donor-acceptor interactions in the NBO basis. The interactions result in a loss of occupancy from the localized NBO of the idealized Lewis structure into an empty non-Lewis orbital. For each donor (i) and acceptor (j) the stabilization energy (E2) associated with the delocalization $i \rightarrow j$ is determined as

$$E(2) = \Delta E_{ij} = q_i \frac{(F_{i,j})^2}{(E_j - E_i)}$$

$q_i \rightarrow$ donor orbital occupancy, E_i , $E_j \rightarrow$ diagonal elements and $F_{ij} \rightarrow$ the off diagonal NBO Fock matrix element

In NBO analysis large E(2) value shows the intensive interaction between electron donors and electron-acceptors, and greater the extent of conjugation of the whole system, the possible intensive interaction are given in Table 3. The second order perturbation theory analysis of Fock-matrix in NBO basis shows strong intermolecular hyper conjugative

interactions are formed by orbital overlap between $n(S)$ and $\sigma^*(C-C)$, $n(O)$ and $\pi^*(C-O)$, $\pi^*(N-C)$ and between $n(N)$ and $\pi^*(N-C)$, $\sigma^*(O-C)$ bond orbitals which result in intra-molecular charge transfer (ICT) causing stabilization of the system. These interactions are observed as an increase in electron density (ED) in C-O, C-C and C-N anti-bonding orbital that weakens the respective bonds. There occurs a strong inter-molecular hyper-conjugative interaction of $C_{15}-C_{16}$ from S_1 of $n_2(S_1) \rightarrow \pi^*(C_{15}-C_{16})$ which increases ED (0.40048e) that weakens the respective bonds $C_{15}-O_{16}$ leading to stabilization of 6.35 KJ/mol and also the hyper-conjugative interaction of O_3-C_{22} from O_2 of $n_2(O_2) \rightarrow \sigma^*(O_3-C_{22})$ which increases ED (0.09135e) that weakens the respective bonds O_3-C_{22} leading to stabilization of 28.89 KJ/mol. Also the hyper-conjugative interaction of O_2-C_{22} from O_3 of $n_2(O_3) \rightarrow \pi^*(O_2-C_{22})$ which increases ED (0.36424e) that weakens the respective bonds O_2-C_{22} leading to stabilization of 48.30 kJ/mol. An another hyper-conjugative interaction observed in O_5-C_{27} from O_4 of $n_2(O_4) \rightarrow \sigma^*(O_5-C_{27})$ which increases ED (0.09305e) that weakens the respective bond O_5-C_{27} leading to a stabilization of 27.39 KJ/mol. An another hyper-conjugative interaction observed in O_4-C_{27} from O_5 of $n_2(O_5) \rightarrow \pi^*(O_4-C_{27})$ which increases ED (0.37514e) that weakens the respective bond O_4-C_{27} leading to a stabilization of 48.44 KJ/mol. Another hyper-conjugative interaction is observed $N_{11}-C_{32}$ from O_6 of $n_2(O_6) \rightarrow \sigma^*(N_{11}-C_{32})$ which increases ED (0.07435e) that weakens the respective bonds $N_{11}-C_{32}$ leading to stabilization of 23.08 KJ/mol. There occurs another strong inter-molecular hyper-conjugative interaction of $N_{10}-C_{21}$ from N_8 of $n_1(N_8) \rightarrow \pi^*(N_{10}-C_{21})$ which increases ED (0.45548e) that weakens the respective bonds $N_{10}-C_{21}$ leading to stabilization of 74.03 KJ/mol. Another hyper-conjugative interaction of O_2-C_{22} from N_9 of $n_1(N_9) \rightarrow \sigma^*(O_2-C_{22})$ which increases ED (0.36424e) leading to a stabilization of 70.40 KJ/mol. Also the hyper-conjugative interaction of O_6-C_{32} from N_{11} of $n_2(N_{11}) \rightarrow \sigma^*(O_6-C_{32})$ which increases ED (0.30056e) that weakens the respective bonds O_6-C_{32} leading to stabilization of 67.88 KJ/mol. These interactions are observed as an increase in electron density C-O, C-C and C-N anti-bonding orbitals that weaken the respective bonds. The increased electron density at the oxygen atoms leads to the elongation of respective bond length and a lowering of the corresponding stretching wave number. The hyper-conjugative interaction energy was deduced from the second-order perturbation approach. Delocalization of electron density between occupied Lewis-type

(bond or lone pair) NBO orbitals and formally unoccupied (anti bond or Rydberg) non-Lewis NBO orbitals corresponds to a stabilizing donor–acceptor interaction. The -OCH_3 and C=O stretching modes can be used as a good probe for evaluating the bonding configuration around the ring. Hence the title compound is stabilized by these orbital interactions. The NBO analysis also describes the bonding in terms of the natural hybrid orbital $n_2(\text{S}_1)$, which occupy a higher energy orbital (-0.22700 a.u) with considerable p-character (100.0%) and low occupation number (1.89282) and the other $n_1(\text{S}_1)$, which occupy a lower energy orbital(-0.61939 a.u) with considerable p-character (30.09%) and high occupation number (1.97699). Also $n_2(\text{O}_2)$, which occupy a higher energy orbital (-0.28710 a.u) with considerable p-character (99.40%) and low occupation number (1.83628) and the other $n_1(\text{O}_2)$, which occupy a lower energy orbital(-0.72302 a.u) with considerable p-character (37.83%) and high occupation number (1.96837). Again $n_2(\text{O}_3)$, which occupy a higher energy orbital (-0.33850 a.u) with considerable p-character (100.0%) and low occupation number (1.80901) and the other $n_1(\text{O}_3)$, which occupy a lower energy orbital (-0.59542 a.u) with considerable p-character (58.51%) and high occupation number (1.96363). Again $n_2(\text{O}_4)$, which occupy a higher energy orbital (-0.27114 a.u) with considerable p-character (98.55%) and low occupation number (1.84593) and the other $n_1(\text{O}_4)$, which occupy a lower energy orbital (-0.69605) with considerable p-character (38.27%) and high occupation number (1.96530). Again $n_2(\text{O}_5)$, which occupy a high energy orbital (-0.30958 a.u) with considerable p-character (100.0%) and low occupation number (1.79828) and the other $n_1(\text{O}_5)$ which occupy a low energy orbital (-0.56611 a.u) with considerable p-character (58.33%) and high occupation number (1.96550). Another $n_2(\text{O}_6)$, which occupy a high energy orbital (-0.22873 a.u) with considerable p-character (100.0%) and low occupation number (1.86864) and the other $n_1(\text{O}_6)$, which occupies a low energy orbital (-0.67269 a.u) with considerable p-character (38.53%) and high occupation number (1.97785). Another $n_2(\text{O}_7)$, which occupy a energy orbital (-0.29788 a.u) with considerable p-character (99.00%) and low occupation number (1.93154) and the other $n_1(\text{O}_7)$, which occupy a low energy orbital (-0.57615 a.u) with considerable p-character (53.96%) and high occupation number (1.96351). Thus, a very close to pure p-type lone pair orbital participates in the electron

donation to the $\sigma^*(\text{C-O})$, $\sigma^*(\text{N-C})$ and $\sigma^*(\text{C-C})$ orbitals in the compound. The results are given in table S1 (supporting material).

4.7. Molecular docking

PASS (Prediction of Activity Spectra) [55] is an online structure activity relationship (SAR) tool which predicts biological activity based on the structure of a molecule. PASS analysis (supplementary table S2) of the Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino)[(methoxycarbonyl)imino] methyl carbamate predicts antihelmintic and antiparasitic activity as the most probable activity with Pa (probability to be active) value of 0.808 and 0.797 respectively. Human African Trypanosomiasis (HAT) is a neglected parasitic disease which has affected millions of rural Africans. Amongst the various targets pteridine reductase (PTR1) serve as a good target to design new drugs to cure HAT [56]. The 3D crystal structure of PTR1 was obtained from Protein Data Bank with accession code 3BMC [57]. Molecular docking simulations were done on AutoDock Vina software [58]. AutoDockTools (ADT) graphical user interface was used to add polar hydrogens and atomic charges by Kollman method. Water molecules and co-crystallised ligands were removed. The Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino)[(methoxycarbonyl)imino] methyl carbamate was prepared for docking by minimizing its energy at B3LYP/6-311++G(d,p) (5D, 7F) level of theory. ADT was employed to add partial charges by Geisteringer method and to define torsions and rotatable bonds. The active site of the enzyme was defined in a manner so as to include residues of the active site within the grid size of $70\text{\AA} \times 70\text{\AA} \times 70\text{\AA}$. Lamarckian Genetic Algorithm (LGA) available in Autodock Vina was employed for docking. The docking protocol was tested by removing co-crystallized inhibitor from the protein and then docking it at the same site. To evaluate the quality of docking results, the common way is to calculate the the Root Mean Square Deviation (RMSD) between the docked pose and the known crystal structure conformation. RMSD values up to $2\text{\AA}$ are considered reliable for a docking protocol [59]. The docking protocol we employed predicted a similar conformation with RMSD value well within the reliable range (Fig.5). Amongst the docked conformations of the title compound, the conformation which was close to the conformation of co-crystallized ligand and scored well was visualized for detailed interactions in Discover Studio

Visualizer 4.0 and Pymol software. The ligand binds at the active site of the protein by weak non-covalent interactions most prominent of which are H-bonding, π - π stacking and alkyl- π interactions (Fig.6). Amino acid Lys178 holds the molecule at the active site by forming H-bond of 2.75Å length with the oxygen of acetyl group. Similarly Arg14 holds the molecule by forming multiple H-bonds with carbonyl oxygen of acetyl and amide groups. Trp221 and Phe97 hold the molecule by π - π t stacking interaction with terminal and central phenyl ring respectively. Pro201 also plays role in stabilizing the ligand-macromolecular complex by forming an alkyl- π interaction with central phenyl ring. Binding free energy (ΔG in kcal/mol) of -9.0 as predicted by autodock vina (supplementary table S3) suggests good binding affinity between the ligand and the target macromolecule. It is evident that both the phenyl groups and the carbonyl oxygens of the molecule are crucial for bonding. These results draw us to the conclusion that the compound might exhibit pteridine reductase inhibitory activity. However biological tests need to be done to validate the computational predictions.

5. Conclusion

FT-IR spectrum of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl) phenyl] amino) [(methoxycarbonyl) imino]methyl)carbamate was recorded and analyzed. Using the Gaussian09 set of quantum chemistry codes, the vibrational wavenumbers are examined theoretically and the normal modes were assigned by potential energy distribution calculations. The HOMO and LUMO analysis are used to determine the charge transfer within the molecule and the HOMO-LUMO energy gap shows the chemical activity of the molecule. The HOMO of π nature is delocalized over the phenyl rings and sulfur atom and in LUMO, only over the phenyl rings. The optimized geometrical parameters are in agreement with XRD data. The stability of the molecule arising from hyper-conjugative interaction and charge delocalization has been studied using NBO analysis. From the MEP plot it is evident that the negative regions are mainly localized over the carbonyl groups and the tri-substituted phenyl ring and the maximum positive regions are localized over the methyl and NH groups. PASS analysis of the title compound predicts antihelmintic and antiparasitic activity as the most probable activity with Pa value of 0.808 and 0.797 respectively. Molecular docking results draw us to the conclusion that the compound might exhibit pteridine reductase inhibitory activity.

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Figure Captions

Fig.1 FT-IR spectrum of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino) [(methoxycarbonyl)imino]methylcarbamate

Fig.2 Optimized geometry of (B3LYP/6-311++G(d,p) (5D, 7F))
Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino)
[(methoxycarbonyl)imino]methyl)carbamate

Fig.3 MEP plot of Methyl N-({[2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino} [(methoxycarbonyl)imino]methyl)carbamate

Fig.4 HOMO and LUMO plots of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino) [(methoxycarbonyl)imino]methyl carbamate

Fig.5 Co-crystallized molecule shown in blue color and the docked conformation (yellow) as predicted by the Autodock Vina show very low RMSD value

Fig.6 The ligand binds at the active site of PTR1. Dotted lines represent the interactions, H bonds, π - π and alkyl- π interactions are represented by green, maroon and violet dotted lines respectively

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Table 1. Optimized geometrical parameters (B3LYP/6-311++G(d,p)(5D, 7F)) of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino)[(methoxycarbonyl)imino]methylcarbamate with XRD data, atom labelling according to Fig.2

Bond lengths (Å)

Label	DFT	XRD	Label	DFT	XRD
C15-S1	1.853	1.7712	C40-S1	1.8549	1.7720
C22-O2	1.2492	1.2081	C22-O3	1.3634	1.3357
C23-O3	1.4722	1.4502	C27-O4	1.2655	1.2289
C27-O5	1.3669	1.3433	C28-O5	1.4669	1.4438
C32-O6	1.2513	1.2296	C33-O7	1.4461	1.4132
C36-O7	1.4490	1.4249	C20-N8	1.4337	1.4288
C21-N8	1.3521	1.3410	N8-H52	1.0212	0.8480
C21-N9	1.3999	1.3752	C22-N9	1.3748	1.3803
N9-H53	1.0287	0.8680	C21-N10	1.3245	1.3241
C27-N10	1.3704	1.3702	N10-H51	1.9085	0.8800
C12-N11	1.4088	1.4129	C32-N11	1.3659	1.3533
N11-H51	1.0241	0.8670	C12-C13	1.4084	1.3968
C12-C20	1.4155	1.4036	C13-H14	1.0804	0.9300
C13-C15	1.3946	1.3894	C15-C16	1.4000	1.3986
C16-H17	1.0832	0.9300	C16-C18	1.3927	1.3868
C18-H19	1.0855	0.9300	C18-C20	1.4039	1.3971
C23-H24	1.0875	0.9600	C23-H25	1.0914	0.9600
C23-H26	1.0914	0.9600	C28-H29	1.0883	0.9600
C28-H30	1.0923	0.9600	C28-H31	1.0921	0.9600
C32-C33	1.5232	1.5136	C33-H34	1.0979	0.9700
C33-H35	1.1013	0.9700	C36-H37	1.0908	0.9600
C36-H38	1.0990	0.9600	C36-H39	1.0985	0.9600
C40-C41	1.4013	1.3943	C40-C49	1.4001	1.3989
C41-H42	1.0843	0.9300	C41-C43	1.3989	1.3905
C43-H44	1.0855	0.9300	C43-C45	1.4013	1.3903
C45-H46	1.0853	0.9300	C45-C47	1.3990	1.3830
C47-H48	1.0855	0.9300	C47-C49	1.4012	1.3933
C49-H50	1.0845	0.9300			

Bond angles (°)

Label	DFT	XRD	Label	DFT	XRD
C15-S1-C40	101.8	105.4	C22-O3-C23	116.6	114.7
C27-O5-C28	116.4	115.1	C33-O7-C36	114.5	110.5
C20-N8-C21	128.5	124.9	C20-N8-H52	116.4	117.2
C21-N8-H52	114.9	117.9	C21-N9-C22	127.0	127.3
C21-N9-H53	113.3	112.4	C22-N9-H53	119.7	120.1

C21-N10-C27	122.1	119.8	C12-N11-C32	127.1	126.4
C12-N11-H51	115.6	116.7	C32-N11-H51	117.2	114.6
N11-C12-C13	121.3	120.9	N11-C12-C20	119.9	119.4
C13-C12-C20	118.8	119.6	C12-C13-H14	118.6	119.9
C12-C13-C15	120.7	120.3	H14-C13-C15	120.6	119.9
S1-C15-C13	117.9	116.3	S1-C15-C16	121.4	123.1
C13-C15-C16	120.6	120.4	C15-C16-H17	120.7	120.4
C15-C16-C18	119.0	119.2	H17-C16-C18	120.3	120.4
C16-C18-H19	119.9	119.5	C16-C18-C20	121.4	121.0
H19-C18-C20	118.7	119.5	N8-C20-C12	124.2	122.4
N8-C20-C18	116.0	118.0	C12-C20-C18	119.5	119.5
N8-C21-N9	117.3	118.5	N8-C21-N10	120.5	118.9
N9-C21-N10	122.3	122.6	O2-C22-O3	123.8	125.8
O2-C22-N9	126.0	125.9	O3-C22-N9	110.2	108.9
O3-C23-H24	104.3	109.5	O3-C23-H25	110.0	109.5
O3-C23-H26	110.0	109.5	H24-C23-H25	111.3	109.5
H24-C23-H26	111.3	109.5	H25-C23-H26	109.7	109.5
O4-C27-O5	121.2	121.0	O4-C27-N10	128.0	129.6
O5-C27-N10	111.0	109.2	O5-C28-H29	104.6	109.5
O5-C28-H30	110.5	109.5	O5-C28-H31	110.4	109.5
H29-C28-H30	111.1	109.5	H29-C28-H31	111.2	109.5
H30-C28-H31	109.1	109.5	O6-C32-N11	126.2	125.5
O6-C32-C33	119.5	119.8	N11-C32-C33	114.3	114.7
O7-C33-C32	110.1	111.9	O7-C33-H34	111.4	109.2
O7-C33-H35	110.7	109.2	C32-C33-H34	108.0	109.2
C32-C33-H35	108.6	109.2	H34-C33-H35	108.0	107.9
O7-C36-H37	106.0	109.5	O7-C36-H38	111.2	109.5
O7-C36-H39	111.2	109.5	H37-C36-H38	109.7	109.5
H37-C36-H39	109.6	109.5	H38-C36-H39	109.1	109.5
S1-C40-C41	121.0	123.7	S1-C40-C49	118.5	116.4
C41-C40-C49	120.4	119.8	C40-C41-H42	120.0	120.3
C40-C41-C43	119.6	119.5	H42-C41-C43	120.4	120.3
C41-C43-H44	119.6	119.5	C41-C43-C45	120.3	121.0
H44-C43-C45	120.1	119.5	C43-C45-H46	120.1	120.3
C43-C45-C47	119.8	119.4	H46-C45-C47	120.1	120.3
C45-C47-H48	120.2	119.8	C45-C47-C49	120.2	120.5
H48-C47-C49	119.6	119.8	C40-C49-C47	119.7	119.9
C40-C49-H50	119.8	120.1	C47-C49-H50	120.5	120.1

Dihedral angles (°)

Label	DFT	XRD	Label	DFT	XRD
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C40-S1-C15-C13	135.6	142.1	C40-S1-C15-C16	-47.5	-43.4
C15-S1-C40-C41	-55.2	-31.9	C15-S1-C40-C49	127.9	152.4
C23-O3-C22-O2	0.1	-1.4	C23-O3-C22-N9	-179.9	178.5
C28-O5-C27-O4	-1.7	1.9	C28-O5-C27-N10	178.5	-178.4
C36-O7-C33-C32	-173.9	-176.4	C21-N8-C20-C12	54.5	61.5
C21-N8-C20-C18	-132.0	123.4	C20-N8-C21-N9	176.7	-178.2
C20-N8-C21-N10	-3.6	0.6	C22-N9-C21-N8	-2.5	-3.4
C22-N9-C21-N10	177.8	178.1	C21-N9-C22-O2	-0.5	-6.3
C21-N9-C22-O3	179.5	173.9	C27-N10-C21-N8	-179.2	-177.8
C27-N10-C21-N9	0.5	0.9	C211-N0-C27-O4	3.1	1.2
C21-N10-C27-O5	-177.1	-178.4	C32-N11-C12-C13	-29.4	-27.6
C32-N11-C12-C20	149.9	155.9	C12-N11-C32-O6	1.1	-15.5
C12-N11-C32-C33	179.9	164.9	N11-C12-C13-C15	180.0	-175.3
C20-C12-C13-C15	0.7	1.2	N11-C12-C20-N8	-6.9	-10.7
N11-C12-C20-C18	179.9	174.3	C13-C12-C20-N8	172.3	172.7
C13-C12-C20-C18	-0.8	-2.3	C12-C13-C15-S1	177.1	175.6
C12-C13-C15-C16	0.2	1.0	S1-C15-C16-C18	-177.6	-176.3
C13-C15-C16-C18	-0.9	-2.1	C15-C16-C18-C20	0.7	1.0
C16-C18-C20-N8	-173.6	-174.0	C16-C18-C20-C12	0.2	1.2
O6-C32-C33-O7	-167.1	-180.0	N11-C32-C33-O7	13.9	-0.3
S1-C40-C41-C43	-177.5	-176.4	C49-C40-C41-C43	-0.7	-0.8
S1-C40-C49-C47	176.7	176.0	C41-C40-C49-C47	-0.2	0.1
C40-C41-C43-C45	0.9	0.5	C43-C45-C47-C49	-0.5	-1.2
C45-C47-C49-C40	0.7	0.9			

Table 2 Calculated (scaled) wavenumbers, observed IR bands and assignments of Methyl N-([2-(2-methoxyacetamido)-4-(phenylsulfanyl)phenyl]amino)[(methoxycarbonyl) imino] methylcarbamate

HF/ 6-31G (6D, 7F) $\nu(\text{cm}^{-1})$ IR _I	B3LYP/ 6-31G (6D, 7F) $\nu(\text{cm}^{-1})$ IR _I	B3LYP/ 6-311+G(d,p) (5D, 7F) $\nu(\text{cm}^{-1})$ IR _I	IR $\nu(\text{cm}^{-1})$	Assignments ^a
3381 228.98	3306 253.58	3333 265.96	3415	$\nu\text{NH}(99)$
3376 319.76	3254 438.34	3326 358.66	3366	$\nu\text{NH}(99)$
3290 264.34	3197 287.31	3211 360.17	3231	$\nu\text{NH}(99)$
3070 0.52	3147 3.82	3100 1.60	3120	$\nu\text{CHII}(99)$
3039 5.34	3112 3.66	3077 1.34	-	$\nu\text{CHII}(99)$
3033 16.08	3106 12.85	3071 9.45	-	$\nu\text{CHI}(100)$
3027 17.63	3101 20.13	3067 12.39	-	$\nu\text{CHI}(94)$
3022 9.71	3093 8.69	3060 13.98	-	$\nu_{\text{as}}\text{CH}_3(99)$
3018 22.04	3092 24.57	3050 6.61	-	$\nu\text{CHI}(96)$
3013 9.07	3081 10.99	3050 6.86	-	$\nu\text{CHII}(96)$
3007 13.57	3081 10.70	3044 10.94	-	$\nu_{\text{as}}\text{CH}_3(96)$
3007 15.86	3079 11.07	3041 0.66	3040	$\nu\text{CHI}(99)$
2996 0.61	3070 0.39	3030 15.83	-	$\nu\text{CHI}(93)$
2992 15.68	3054 15.07	3012 14.80	-	$\nu_{\text{as}}\text{CH}_3(100)$
2976 20.54	3043 12.23	3000 18.28	-	$\nu_{\text{as}}\text{CH}_3(90)$
2975 26.86	3040 25.59	2996 22.92	2980	$\nu_{\text{as}}\text{CH}_3(98)$
2908 26.15	2968 25.58	2939 33.83	2942	$\nu_{\text{as}}\text{CH}_3(100)$
2907 23.06	2959 39.42	2929 47.70	-	$\nu_{\text{s}}\text{CH}_3(98)$
2906 48.09	2957 39.46	2914 19.55	-	$\nu_{\text{s}}\text{CH}_3(96)$
2898 33.01	2950 39.11	2908 52.71	2912	$\nu_{\text{as}}\text{CH}_2(97)$
2860 23.85	2898 62.32	2871 62.87	-	$\nu_{\text{s}}\text{CH}_2(44),$ $\nu_{\text{s}}\text{CH}_3(52)$
2847 50.90	2893 29.48	2864 50.67	2870	$\nu_{\text{s}}\text{CH}_2(56),$ $\nu_{\text{s}}\text{CH}_3(40)$
1670 113.66	1653 750.42	1696 291.03	-	$\delta\text{NH}(46),$ $\nu\text{C}=\text{N}(18),$ $\nu\text{C}=\text{O}(17)$
1654 808.05	1647 92.43	1679 233.24	1673	$\delta\text{NH}(49),$ $\nu\text{C}=\text{O}(17)$
1644 141.16	1634 179.33	1618 755.57	1624	$\delta\text{NH}(13),$ $\nu\text{C}=\text{O}(69)$
1619 750.69	1598 559.51	1602 651.08	1600	$\delta\text{NH}(46),$ $\nu\text{C}=\text{O}(45)$
1611 82.76	1586 56.21	1567 184.51	1565	$\nu\text{PhII}(64)$

1597	25.95	1576	9.21	1563	114.49	1565	ν PhI(70), δ CHI(19)
1591	228.83	1575	11.13	1558	13.26	-	ν PhI(71), δ CHI(10)
1591	55.27	1568	409.89	1551	2.28	1550	ν PhII(43), δ NH(21)
1559	130.18	1528	67.96	1532	331.43	1540	ν C=O(53), ν CN(16)
1534	446.69	1518	367.37	1487	430.57	1477	δ NH(24), ν PhII(26), δ CHII(10)
1497	56.72	1489	13.43	1456	39.72	1458	δ CH ₃ (65), δ CH ₂ (23)
1491	11.93	1482	25.76	1450	9.25	-	ν PhII(44), δ CHII(36)
1489	21.12	1477	31.71	1449	21.65	1449	ν PhI(50), δ CHI(20), δ CH ₃ (10)
1482	67.81	1477	20.04	1442	37.70	-	δ CH ₃ (59)
1480	65.41	1476	12.26	1441	10.39	-	δ CH ₃ (77)
1479	10.56	1472	8.69	1433	17.29	-	δ CH ₃ (33), δ CH ₂ (48)
1477	20.87	1470	42.32	1430	47.73	-	δ CH ₃ (70), δ CH ₂ (17)
1473	6.42	1463	10.77	1428	414.69	1430	δ CH ₃ (94)
1471	11.73	1462	5.67	1428	24.43	-	δ CH ₃ (93)
1468	810.02	1455	745.20	1427	8.16	-	δ CH ₃ (20), ν C=N(39), δ NH(11)
1456	166.57	1442	6.23	1418	97.86	-	ν PhI(67), δ CHI(16)
1453	31.37	1441	45.41	1413	14.76	-	δ CH ₃ (76)
1445	10.29	1435	97.87	1412	4.67	-	δ CH ₃ (73)
1441	495.39	1424	329.32	1398	471.78	1399	δ CH ₃ (55), δ NH(14)
1402	74.99	1400	124.40	1376	126.87	1374	ν PhII(46), δ CHII(19), ν CN(15)
1375	86.64	1352	621.41	1334	12.09	1332	ν CN(42)
1368	961.71	1349	8.88	1315	496.70	-	δ CH ₂ (79)

1337	2.77	1324	2.10	1293	1.46	1295	ν PhI(18), δ CHI(65)
1308	92.90	1307	100.64	1270	117.39	-	ν PhII(67), ν PhI(12)
1298	228.98	1300	63.26	1262	41.03	-	ν PhI(52), ν PhII(15)
1278	675.37	1297	70.74	1253	71.54	-	ν CN(18), δ CHII(50)
1270	246.28	1278	12.70	1252	95.82	-	ν CN(39), δ CHII(20)
1253	6.30	1242	561.70	1220	508.31	1222	ν CN(22), ν CO(37)
1230	11.76	1233	316.04	1210	47.81	-	ν CN(45), δ NH(14)
1220	0.35	1229	20.66	1203	486.46	1206	ν CC(15), ν CN(41), ν PhII(17)
1208	74.42	1208	49.19	1197	53.10	-	ν CN(40), δ CHII(35)
1193	33.06	1197	11.88	1185	70.63	1188	δ CH ₂ (86)
1188	0.40	1186	2.82	1168	8.47	1170	ν PhI(14), δ CHI(78)
1185	63.63	1175	0.07	1167	10.29	-	ν PhI(11), δ CHI(80)
1182	43.91	1162	19.08	1164	102.14	1164	ν CO(74)
1175	13.47	1160	39.72	1154	2.46	1149	ν CO(78)
1146	2.13	1157	101.49	1136	0.04	-	δ CH ₃ (86)
1145	2.32	1135	5.25	1129	0.61	-	ν PhII(16), δ CHII(48)
1144	0.34	1124	0.96	1129	2.37	-	δ CH ₃ (56)
1141	3.25	1124	0.05	1127	0.74	-	δ CH ₃ (49)
1125	6.90	1121	0.30	1112	8.54	1118	δ CH ₃ (52), ν CN(20)
1120	142.93	1095	78.37	1096	217.47	1104	ν CN(18), ν CO(40)
1100	155.83	1078	55.75	1094	119.88	1090	ν PhII(25), δ CHII(47)
1090	3.68	1073	3.05	1065	6.19	1063	ν PhI(24), δ CHI(54)
1076	14.33	1066	28.71	1055	14.11	-	ν PhI(17),

							ν CN(56)
1070	2.21	1062	96.03	1053	9.23	-	ν CO(79)
1064	1.17	1019	248.86	1044	196.05	1046	ν CO(39), ν CN(24)
1048	234.40	1018	30.43	1003	15.74	1009	ν PhI(25), δ CHI(43)
1038	0.83	1008	10.35	985	7.45	987	δ CH ₂ (74), γ C=O(12)
1029	5.64	994	1.99	976	2.20	978	δ PhI(17), γ CHI(12), ν PhI(49)
1026	4.63	992	0.15	967	0.15	-	γ CHI(75), τ PhI(15)
1021	15.87	965	0.13	965	51.42	-	γ CHI(91)
992	3.06	959	33.32	962	24.80	-	ν CC(16), δ PhII(16)
988	21.00	951	22.58	951	0.10	954	γ CHII(21)
982	2.50	947	5.17	940	9.32	-	γ CHII(64), τ PhII(12)
965	19.21	924	27.99	936	6.84	937	δ PhII(12), ν CO(22)
954	16.11	919	190.31	926	2.00	-	γ NH(43), τ NH(20), τ C=O(12)
950	341.02	916	1.83	913	6.64	912	γ CHI(85)
942	73.55	911	27.19	895	2.59	-	γ CHII(21), δ CH ₃ (57)
930	11.56	907	6.62	891	28.80	882	γ CHII(15), δ CH ₃ (48)
912	6.48	898	10.44	859	9.20	855	ν CO(11), γ CHII(48)
892	4.76	879	2.34	838	9.03	836	ν CO(19), ν CN(10), δ C=N(11)
890	0.63	862	85.77	822	0.12	-	γ NH(37), δ NH(15), τ C=O(14)
881	28.56	843	3.67	810	75.98	811	γ CHI(88)
864	120.65	840	36.98	789	19.62	786	γ CHII(19), γ CN(24)

838	13.03	812	74.10	774	20.27	777	γ NH(40), τ NH(18), τ C=N(11)
808	99.59	806	11.88	755	47.47	760	γ CHII(52), γ NH(18)
787	36.15	751	32.64	751	15.74	-	τ PhI(30), τ CS(10), γ CHI(53)
773	12.69	736	2.71	742	22.60	744	ν PhII(51), δ C=O(10)
757	13.97	735	7.15	732	32.30	735	γ C=O(43), τ PhII(11)
746	3.46	727	3.83	730	14.69	-	τ PhII(19), γ CN(18), γ C=O(11)
736	16.55	716	3.88	703	2.71	705	τ PhII(40), γ CN(29)
728	11.96	702	7.17	697	8.87	-	γ C=O(58), γ NH(18)
715	56.19	696	37.07	685	22.68	685	τ PhI(25), γ CHI(26), ν CS(38)
693	13.72	682	8.27	677	8.70	-	δ PhI(55), ν CS(24)
687	8.86	676	4.38	676	24.25	676	γ C=N(63), τ NH(27)
683	7.15	669	9.74	662	24.70	665	δ PhII(32), δ C=O(33)
671	5.11	659	2.02	649	21.12	642	δ PhII(20), δ C=O(41)
636	32.58	622	0.16	606	0.14	607	δ PhI(88)
624	0.42	617	17.03	601	16.18	601	γ CS(16), τ PhII(60), γ CN(14), γ C=O(12)
594	5.99	593	6.19	589	4.85	586	δ C=O(29), γ CN(21), τ PhII(22)
579	11.65	566	0.35	562	1.03	564	γ C=O(38),

555	15.92	553	6.72	551	9.64	549	γ CN(16), τ PhII(16) δ CN(29), δ C=O(16), τ PhII(18)
527	15.95	522	21.40	522	20.60	520	δ PhII(14), δ C=O(35)
505	16.78	493	12.21	493	13.49	-	τ PhI(33), τ CS(21)
485	6.33	474	1.22	468	0.59	-	τ PhII(15), γ CN(24), δ CN(11)
459	11.42	449	3.86	444	2.47	-	τ PhII(30), γ CN(16)
445	9.39	431	9.11	431	5.52	-	τ PhII(25), δ CN(12), δ C=O(10)
421	2.88	418	8.83	423	7.38	-	ν CS(31), τ PhI(10)
417	0.57	409	0.41	405	8.08	-	τ PhI(69)
399	1.16	403	0.78	397	0.97	-	τ PhI(41), γ CS(15)
366	22.57	377	21.84	387	17.64	-	δ CO(33), δ C=N(26), δ C=O(22)
359	4.15	348	7.93	352	24.56	-	δ C=O(14), δ CN(23), γ CS(18)
337	32.76	341	25.47	337	10.36	-	τ PhII(18), δ CO(17), δ CN(21)
301	0.40	309	0.78	309	0.21	-	δ CO(35), δ C=O(11), τ PhII(13)
287	3.31	279	11.84	282	12.78	-	δ CO(29), δ C=O(15), τ PhII(19)
271	15.67	273	12.35	273	4.73	-	δ CS(38), δ NH(14), δ C=O(17)

269	7.99	269	14.27	264	18.11	-	δ CS(22), δ NH(18), δ CO(16)
259	0.79	258	0.28	254	0.50	-	τ C=N(21), τ NH(22), τ C=O(10)
250	11.12	245	7.33	237	2.08	-	γ NH(11), δ C=N(11), δ C=O(10), δ CO(11)
245	15.57	240	2.05	230	1.61	-	τ PhII(33), γ CS(17), τ PhII(25)
220	5.42	229	2.31	221	1.53	-	τ CH ₃ (87)
213	3.57	222	5.13	212	2.58	-	δ C=O(26), δ CO(24), τ CH ₃ (22)
192	4.59	209	6.22	199	6.66	-	τ C=N(18), τ PhI(15), τ CO(19)
190	10.59	185	4.96	176	4.90	-	τ CO(26), τ NH(17), τ PhI(28)
166	0.84	170	0.12	168	0.44	-	τ PhI(47), τ CS(15)
143	7.92	142	5.55	141	3.81	-	τ CH ₂ (21), τ CO(18), τ NH(14)
131	2.35	131	2.56	132	0.22	-	τ CO(27), τ CH ₃ (13), τ NH(16), τ C=N(13)
125	0.30	127	0.38	123	2.25	-	δ CH ₂ (18), τ PhII(22), τ C=O(16)
119	0.35	116	0.07	119	0.78	-	γ NH(14), δ C=N(13), τ CH ₃ (18), τ C=O(12)
106	2.55	104	3.05	109	1.18	-	τ PhII(31),

							$\tau\text{C}=\text{O}(15),$ $\tau\text{NH}(11),$ $\tau\text{CN}(10)$
101	3.90	99	8.68	103	3.61	-	$\tau\text{CH}_3(49),$ $\tau\text{CH}_2(25)$
97	2.29	95	0.72	94	1.54	-	$\tau\text{CH}_3(40),$ $\tau\text{CH}_2(14),$ $\tau\text{CO}(14)$
88	2.23	88	0.44	89	0.57	-	$\delta\text{CN}(19),$ $\tau\text{C}=\text{O}(11),$ $\delta\text{C}=\text{O}(10),$ $\delta\text{C}=\text{N}(11)$
84	5.15	87	1.59	81	2.27	-	$\tau\text{NH}(48),$ $\tau\text{PhII}(18)$
79	2.24	74	0.74	76	0.81	-	$\tau\text{CH}_3(25),$ $\tau\text{NH}(33)$
69	6.46	67	1.03	62	3.71	-	$\tau\text{NH}(20),$ $\tau\text{CO}(15),$ $\tau\text{CH}_3(15),$ $\tau\text{C}=\text{O}(12)$
63	1.12	67	3.83	59	1.65	-	$\tau\text{C}=\text{O}(25),$ $\tau\text{CH}_3(21),$ $\tau\text{CH}_2(19)$
51	0.76	53	1.03	49	1.55	-	$\delta\text{NH}(26),$ $\delta\text{CS}(18),$ $\tau\text{C}=\text{O}(25)$
46	0.86	47	0.18	45	0.40	-	$\tau\text{NH}(37),$ $\tau\text{C}=\text{O}(30)$
36	1.58	38	1.67	31	0.01	-	$\tau\text{NH}(17),$ $\tau\text{C}=\text{N}(15),$ $\tau\text{C}=\text{O}(10),$ $\tau\text{CH}_2(10)$
29	0.38	34	1.41	28	0.88	-	$\tau\text{NH}(40),$ $\tau\text{C}=\text{O}(11),$ $\tau\text{C}=\text{N}(10)$
26	0.72	24	0.39	24	1.07	-	$\tau\text{PhII}(27),$ $\tau\text{NH}(16),$ $\tau\text{C}=\text{N}(18)$
20	0.84	22	0.79	23	0.19	-	$\tau\text{CS}(44),$ $\delta\text{CS}(10)$

18	0.32	17	0.51	18	0.46	-	τ NH(27), τ C=N(12), τ CS(13)
14	0.68	7	0.87	4	1.03	-	τ CS(81)

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; as-asymmetric; s-symmetric; potential energy distribution is given in brackets in the assignment column; PhI-mono substituted phenyl ring; PhII-tri-substituted phenyl ring; IR_I-IR intensity in KM/mole/

Table 3. 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
N10-C21	π	1.82411	O4-C27	π^*	0.37514	35.41	0.31	0.098
-	π	-	N10-C21	π^*	0.45548	6.22	0.30	0.042
C12-C13	π	1.62598	C15-C16	π^*	0.40048	21.12	0.27	0.068
-	π	-	C18-C20	π^*	0.40407	20.21	0.27	0.066
C15-C16	π	1.65245	C12-C13	π^*	0.36908	20.18	0.28	0.068
-	π	-	C18-C20	π^*	0.40427	21.43	0.27	0.069
C18-C20	π	1.68043	C12-C13	π^*	0.36908	19.34	0.29	0.068
-	π	-	C15-C16	π^*	0.40048	18.74	0.28	0.066
C40-C49	π	1.67791	C41-C43	π^*	0.31287	19.43	0.29	0.067
-	π	-	C45-C47	π^*	0.32792	18.71	0.29	0.066
LPS1	π	1.89282	C15-C16	π^*	0.40048	6.35	0.25	0.039
-	-	-	C40-C49	σ^*	0.02314	4.68	0.25	0.033
LPO2	π	1.83628	O3-C22	σ^*	0.09135	28.89	0.62	0.121
-	-	-	N9-C22	σ^*	0.06933	18.69	0.71	0.105
LPO3	σ	1.96363	O2-C22	σ^*	0.02446	8.57	1.10	0.087
LPO3	π	1.80901	O2-C22	π^*	0.36424	48.30	0.30	0.113
LPO4	σ	1.96350	N10-C27	σ^*	0.05594	5.14	1.17	0.070
LPO4	π	1.96530	O5-C27	σ^*	0.09305	27.39	0.63	0.119
LPO4	π	1.84593	N10-C27	σ^*	0.05594	14.41	0.74	0.095
LPO5	σ	1.96550	O4-C27	σ^*	0.03882	7.70	1.07	0.081
LPO5	π	1.79828	O4-C27	π^*	0.37514	48.44	0.30	0.112
LPO6	π	1.86864	N11-C32	σ^*	0.07435	23.08	0.72	0.116
LPO6	π	-	C32-C33	σ^*	0.06038	18.68	0.61	0.097
LPN8	σ	1.64226	N10-C21	π^*	0.45548	74.03	0.25	0.124
LPN8	σ	-	C18-C20	π^*	0.40407	13.49	0.29	0.057
LPN9	σ	1.64716	O2-C22	π^*	0.36424	70.40	0.25	0.118
LPN9	σ	-	N10-C21	π^*	0.45548	54.63	0.26	0.110
LPN10	σ	1.86215	O4-C27	σ^*	0.03882	12.16	0.84	0.093
-	σ	-	N9-C21	σ^*	0.05156	15.80	0.74	0.098
LPN11	σ	1.64290	O6-C32	π^*	0.30056	67.88	0.26	0.120
-	σ	-	C12-C13	π^*	0.36908	24.02	0.28	0.073

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

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

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

Graphical abstract

Highlights

- * IR, spectrum and theoretical analysis were reported.
- * The IR spectrum was predicted by theoretically..
- * The wavenumbers are assigned using PED analysis.
- * The calculated energy gap reveals the molecular activity of the title compound.
- * Molecular docking predicted pteridine reductase inhibitory activity. activity for the title compound.