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Graphical abstract

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Spectroscopic, DFT, molecular dynamics and molecular docking study of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide based on DFT calculations

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Abstract

FT-IR and FT-Raman spectrum of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide were recorded and theoretical study has been made using Gaussian09 software package. DFT/B3LYP calculations have been done using 6-311++G (d, p) (5D, 7F) basis sets to investigate the vibrational frequencies and geometrical parameters. The assignments of the normal modes are done by potential energy distribution (PED) calculations. First and second hyperpolarizabilities are calculated in order to find its role in non-linear optics. The stability of the molecule arising from hyper-conjugative interaction and charge delocalization has been analyzed using NBO analysis. Molecular Electrostatic Potential was calculated by the DFT method and predicts the most reactive part in the molecule. The calculated NMR values are in good agreement with experimental data. Reactive sites of the title molecule have been determined by calculations of average local ionization surfaces and Fukui functions. Analyzing electron density between atoms, intra-molecular non-covalent interactions have been determined. Possible locations prone to autoxidation and locations where degradation could start have been determined by calculation of bond dissociation energies for all single acyclic bonds. Atoms with pronounced interactions with water molecules have been located by calculations of radial distribution functions, obtained after molecular dynamics simulations. The docked title compound forms

a stable complex with CDK inhibitor and gives a binding affinity value of -6.3 kcal/mol and the results suggest that the compound might exhibit inhibitory activity against CDK inhibitor.

Keywords: DFT; Imidazole; ALIE; BDE; MEP; Molecular docking.

1. Introduction

Imidazole is an aromatic heterocyclic compound of colourless to pale yellow crystalline solid with a weak amine like odor and is soluble in water. The simplest member of the imidazole family is imidazole itself [1]. The imidazole scaffold is forecasted to be a good pharmacophore and represents an important synthetic precursor in new drug discovery [2-4]. These scaffolds play very important role as mediators in synthetic reactions, primarily for preparing functionalized materials [5-7]. Most of the imidazole derivatives are present in antibacterial, antifungal, antiprotozoal, antihelminthic, anti-HIV, antimicrobial, anti-convulsant, antitubercular, medications [8-13] and it act as a potential anticancer agent [14]. In addition, imidazoles have been used extensively as metal corrosion inhibitors [15] fire retardant, powerful explosives, photography, dyes and agricultural chemicals [16, 17]. Imidazole derivatives have attracted considerable attention because of the unique optical properties [18] and also have significant analytical applications due to their fluorescence properties [19]. Imidazole in polymers has traditionally been utilized in a variety of applications such as immobilized catalysts [20, 21], redox reactions [22], water purifications [23, 24], hydrometallurgy /metal recovery [25, 26] ion and proton conductors [27]. They also have applications in biochemical processes, catalysis, electron transport systems and nanoparticle electron synthesis [28]. Hasegawa *et al.* [29] have reported vibrational spectra and ab initio DFT calculations of 4-methylimidazole and its different protonated forms. Sudha *et al.*, [30] reported the molecular structures, vibrational spectroscopic, first order hyperpolarizability of 2-aminobenzimidazole.

In the present work, theoretical calculations were carried out by DFT (B3LYP) with the use of 6-31G (d) (6D, 7F) and 6-311++G (d, p) (5D, 7F) basis sets. Also FT- IR, FT-Raman and NMR parameters of the title compound are described both experimentally and theoretically. Great amount of compounds based on biologically active molecules end up as organic environmental pollutants. These compounds are especially dangerous for water resources because they are toxic for aquatic organisms [31, 32]. So far conventional methods for water purification turned out to be inefficient for pharmaceutical compounds based on biologically active molecules and there is necessity for development of economical procedures that could advance the degradation of these compounds [33-35]. Advanced oxidation processes are seen as efficient alternative for the problem of degradation of organic

pollutants [36, 37]. Investigation of degradation properties of organic compounds is long and tedious task. However, DFT calculations and MD simulations are seen as reliable help which can be used for determination of possible molecule sites prone to autoxidation and to interaction with water molecules. Particularly, calculations of bond dissociation energies (BDE) can be used for detection of not only sites prone to autoxidation but also for detection of the weakest bonds which could be broken with lower amounts of energy. On the other side, calculations of radial distribution functions reveal which atoms have the most pronounced interactions with water molecules, which helps in understanding the influence of hydrolysis in degradation process. Molecular docking studies are also reported due to various biological properties of the title compound.

2. Experimental details

1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide was synthesized via a solvent free procedure as shown in Scheme 1. 10 mmole (1.01 g) of 3-(hydroxyimino) butan-2-one was mixed with 10 mmole (1.36 g) of 4-hydroxybenzaldehyde and 15 mmole (1.5 ml) of n-butyl amine in an agate mortar and grinded thoroughly for 2 minutes with a pestle into an intimate mixture and subsequently heated in an oil bath at 115-120 °C, when a melt was formed. After further 8 minutes of heating, the completion of the reaction was indicated by thin layer chromatography (TLC), performed using 0.25 mm Merck Aluminium silica gel 60-F254 precoated plates. On cooling the melt slowly solidified and to the product so formed was added a little amount of ether whereby a precipitate was obtained. The precipitate was further washed with hot ethyl acetate (Scheme Fig.S1, supporting material). Recrystallization from ethanol gave a product with the same melting point.

The FT-IR (Fig. S2- supporting material) and FT-Raman spectra (Fig. S3- supporting material) were recorded using KBr pellets on a DR/Jasco FT-IR 6300 spectrometer and Bruker RFS 100/s, Germany. ^1H and ^{13}C NMR were recorded in dmsO-d_6 on a Bruker Avance 300 spectrometer. The electrospray mass spectrum was recorded on a MICROMASS QUATTRO II triple quadrupole mass spectrometer. The ESI capillary was set at 3.5 kV and cone voltage was 40V. ESI m/z found for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$: 260.15 (M+1). Melting Point (uncorrected): 128-130°C. Anal./Calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$: C, 69.20; H, 7.74; N, 10.76; O, 12.29; Found: C, 69.12; H, 7.81; N, 10.52; O, 12.45.

3. Computational details

The wave numbers of the title compound were carried out with Gaussian09 [38] program using the B3LYP/6-311++G (d, p) (5D, 7F) level of theory and a scaling factor of 0.9613 has to be used for obtaining a considerably better agreement with experimental data

[39]. The 6-311++G basis set [40-42] was chosen particularly because of its advantage of doing faster calculations with relatively better accuracy and structures [43]. Parameters corresponding to optimized geometry (B3LYP) of the title compound (Fig.1) are given in Table 1. The assignments of the calculated frequencies are aided by GAUSSVIEW program [44] and GAR2PED software package [45]. The NMR and HOMO-LUMO energy data were obtained from the DFT method using basis set B3LYP/6-311++G (d, p) (5D, 7F).

In this work for the theoretical analysis of title molecule Schrödinger Materials Science Suite 2015-4 [46] has been used as well. Jaguar 9.0 program [47] was used for DFT calculations, while Desmond program [48-51] was used for molecular dynamics simulations. B3LYP [42] exchange-correlation functional has been employed for calculation of average local ionization energy (ALIE) surfaces, Fukui functions and BDE with 6-311++G(d,p), 6-31+G(d) and 6-311G(d,p) basis sets, respectively. BDE have been calculated for all single acyclic bonds, while method of Johnson et al. [52, 53] was used for investigation of intramolecular noncovalent interactions. OPLS 2005 force field [54] was used for MD simulations, within NPT ensemble. Pressure and temperature were set to 1.0325 bar and 300 K, respectively. Simulation time was 5 ns with cut off radius set to 12 Å. System investigated with MD approach was modeled in such way that one title molecule was placed in cubic box with ~3000 water molecules. Solvent was treated within the simple point charge (SPC) model [55].

4. Results and Discussion

In the following discussion the phenyl ring and imidazole ring are designated as Ph and Ring and the experimentally results are compared with the values given by B3LYP/6-311++G (d, p) (5D, 7F) values.

4.1. Geometrical parameters

From the table 1, the C-C bond length of C₆-C₁₁ (1.458 Å) is greater than that of C₅-C₆ (1.407 Å) and C₁-C₆ (1.406 Å), because of the delocalization of electron density of C₆-C₁₁ with the ring in which N-O is substituted. Also the slight difference in the bond lengths of C₂-C₃ (1.394 Å), C₃-C₄ (1.396 Å) is due to the presence of -OH group in the neighbourhood. The C-N bond lengths C₁₁-N₁₄ (1.354 Å), C₁₁-N₁₅ (1.383 Å), C₁₂-N₁₅ (1.388 Å) and C₁₃-N₁₄ (1.394 Å) are different because of the difference in their environment and also assume a double bond character in C₁₁-N₁₄. The bond angle between C₆-C₁₁-N₁₄ (124.5°) and C₆-C₁₁-N₁₅ (128.4°) indicates the better delocalization in the former. Also C₁₁-N₁₄-C₁₃ (109.3°) and C₁₁-N₁₅-C₁₂ (108.8°) indicates slightly higher electronegative property of oxygen atom.

The CC bond lengths are in the range 1.389-1.407 Å in the phenyl ring, 1.370 Å, in Ring, 1.493, 1.486 Å among -CCH₃ part, 1.536, 1.537 and 1.534 Å in butyl group and 1.458 Å in the carbon-carbon bridge respectively. The CH bond lengths are 1.081-1.086 Å in phenyl ring and 1.090-1.095 Å for the CH₃ groups. The CH bond lengths are in the range 1.090-1.097 Å for the CH₂ groups. The butyl group is tilted from the Ring, as is evident from torsion angles, C₁₃-C₁₂-N₁₅-C₂₇ (-169.8°), N₁₄-C₁₁-N₁₅-C₂₇ (169.0°), C₁₁-N₁₅-C₂₇-C₃₀ (108.5°) and C₁₂-N₁₅-C₂₇-C₃₀ (-83.9°). At N₁₄ position, the bond angles C₁₁-N₁₄-O₂₄ = 127.1°, C₁₃-N₁₄-O₂₄ = 123.4° and C₁₁-N₁₄-C₁₃ = 109.3° and this asymmetry of angles reveal the double bond character of N-O and its conjugation with the C=C bond and at N₁₅ position, the bond angles C₁₁-N₁₅-C₂₇ = 125.8°, C₁₂-N₁₅-C₂₇ = 124.3° and C₁₁-N₁₅-C₁₂ = 108.8° and this asymmetry of angles reveal the steric repulsion of the atoms H₂₈, H₂₉ [56].

The aromatic ring of the title compound is somewhat irregular and the spread of CC bond distance is 1.389-1.407 Å in phenyl ring, Smith *et al.*, [57] also reported similar spread. Chambers *et al.*, [58] reported the C-N length as 1.454 Å and the experimental values of C-N lengths in the range 1.442-1.460 Å [59]. Sundaraganesan *et al.*, [60] reported C-N bond lengths as 1.453, 1.460 Å (SDD). For the title compound, the C-N bond lengths are 1.354, 1.383, 1.388, 1.394 Å, which are in agreement with the reported values. Purkayastha and Chattopadhyay reported N=C, N-C bond lengths as 1.327, 1.400 Å for benzothiazole and 1.350, 1.407 Å for benzimidazole compounds [61].

The carbon-oxygen C₃-O₂₅ distance of 1.368 Å is in agreement with the average distance of 1.362 Å found among phenols [62]. The CC bond lengths for the butyl group C₂₇-C₃₀ = 1.536, C₃₀-C₃₃ = 1.537 and C₃₃-C₃₆ = 1.534 Å which are in agreement with the reported values [63]. For the di-substituted phenyl ring, C-C bond lengths are in the range 1.389-1.407 Å. Here for the title compound, benzene rings are a regular hexagon with bond lengths somewhere in between the normal values for single (1.40 Å) and double (1.38 Å) bond [64].

4.2. IR and Raman spectra

The observed IR and Raman bands and calculated (scaled) wavenumbers and assignments are given in Table 2.

CH₂ Modes

The vibrations of the CH₂ group (the asymmetric stretch, symmetric stretch, scissoring vibration and the wagging vibration) appear in the regions 2940 ± 20, 2885 ± 45, 1440 ± 10 and 1340 ± 25 cm⁻¹, respectively [65, 66]. The CH₂ stretching bands are observed at 2928, 2869 cm⁻¹ in the IR spectrum, 2935 cm⁻¹ in the Raman spectrum and in the range 2991-2897 cm⁻¹ theoretically. The deformation modes of CH₂ groups are observed at 1453,

1283, 1246, 1211, 1100 cm^{-1} in the IR spectrum and at 1460, 1443, 1363, 1334, 1292, 1281, 1262, 1243, 1215, 1125 cm^{-1} in the Raman spectrum. Theoretical calculations give these modes in the range 1454-1115 cm^{-1} . The bands at 778, 751, 729 cm^{-1} in the IR spectrum, 776, 743, 727 cm^{-1} in Raman spectrum and at 776, 753, 725 cm^{-1} (DFT) are assigned as rocking modes of CH_2 , for the title compound. The torsion modes of CH_2 are seen in low wave number range [65].

CH₃ modes

In aromatic methoxy compounds, the methyl stretching vibrations are expected in the region 3010-2900 cm^{-1} (asymmetric) and 2950-2850 cm^{-1} (symmetric) [65]. In the present case the DFT calculations give methyl stretching vibrations in the range 3001-2902 cm^{-1} and experimentally bands are observed at 2959, 2928 cm^{-1} in the IR spectrum and at 2994, 2970, 2935, 2908 cm^{-1} in the Raman spectrum. The methyl deformation modes are observed at 1402, 1069, 1021 cm^{-1} in the IR spectrum, 1443, 1411, 1363, 1078, 937 cm^{-1} in the Raman spectrum and in the range 1451-928 cm^{-1} theoretically which are in agreement with literature [65].

O-H group

The O-H stretching vibration is expected in the range $3380 \pm 200 \text{ cm}^{-1}$ [65]. For the title compound the O-H stretching appears at 3665 cm^{-1} in the IR spectrum and at 3685 cm^{-1} theoretically (DFT). Krishnakumar *et al.*, [67] reported the O-H stretching vibration appears at 3661 cm^{-1} in IR spectrum and 3661 cm^{-1} theoretically (DFT). The in-plane O-H deformation [65] is expected in the region $1440 \pm 40 \text{ cm}^{-1}$ and for the title compound the band assigned at 1316 cm^{-1} theoretically (DFT). The reported values of O-H in-plane deformation is at 1345 cm^{-1} [68] and at 1318 cm^{-1} [69].

C-O modes

For the title compound, the stretching of C-O appears at 1230 cm^{-1} in Raman spectrum and the calculated value is 1234 cm^{-1} (DFT) and this band is not pure, but contains significant contributions from other modes also. This band is expected in the region $1220 \pm 40 \text{ cm}^{-1}$ [66, 70, 71]. Varghese *et al.*, [68] reported C-O stretching at 1255 cm^{-1} in both IR and Raman spectra and 1262 cm^{-1} theoretically. Ulahannan *et al.*, [72] reported that the stretching of C-O at 1215 cm^{-1} in IR and 1208 cm^{-1} theoretically.

N-O, C=N and C-N modes

According to literature, nitroxide radical shows that N-O stretching mode lies between 1340 and 1380 cm^{-1} [73] or near 1350 cm^{-1} [74], with other reported data lying between 1310 cm^{-1} and 1370 cm^{-1} [73]. The accepted band position of $\nu\text{N-O}$ is considerably less than

$\nu\text{N=O}$ ($1600\text{--}1500\text{ cm}^{-1}$) [75] but greater than $\nu\text{N-O}$ in oximes ($965\text{--}930\text{ cm}^{-1}$) [76] in accordance with its bond and a half character [77]. For the title compound, DFT calculations give the $\nu\text{N-O}$ mode at 1305 cm^{-1} . The C=N stretching modes were reported at $1535\text{--}1666\text{ cm}^{-1}$ [78]. In the present case the DFT calculation give C=N stretching mode at 1425 cm^{-1} . This is in agreement with the literature Benzon *et al.* [79]. According to Silverstein *et al.*, [71] C-N stretching modes are expected in the region $1382\text{--}1266\text{ cm}^{-1}$ for aromatic amines. In the present case, the νCN stretching modes are observed at $1341, 1171\text{ cm}^{-1}$ in the IR spectrum, $1292, 1171\text{ cm}^{-1}$ in the Raman spectrum and in the range $1346\text{--}1153\text{ cm}^{-1}$ theoretically. Renjith *et al.*, [80] reported the νCN stretching at $1343, 1364\text{ cm}^{-1}$ (Raman), $1340, 1363\text{ cm}^{-1}$ (IR), $1328, 1343, 1364\text{ cm}^{-1}$ (DFT) and Bhagyasree *et al.*, [81] reported C-N stretching vibrations are observed in the region $1228\text{--}1195\text{ cm}^{-1}$.

C=C and C-C vibrations

The C=C stretching vibrations give rise to characteristic bands in the spectral region ranging from $1650\text{--}1430\text{ cm}^{-1}$ [82]. In the present case the C=C stretching vibrations are observed at 1606 cm^{-1} (IR), 1604 cm^{-1} (Raman) and assigned at 1606 cm^{-1} (DFT), respectively. Felfoldi *et al.*, [83] reported the C=C stretching vibration at 1625 cm^{-1} theoretically. In the present case C-C stretching vibrations are observed at $1385, 1283, 1069\text{ cm}^{-1}$ (IR), $1385, 1334, 1281, 1078, 1030\text{ cm}^{-1}$ (Raman) and in the range $1395\text{--}943\text{ cm}^{-1}$ theoretically.

Phenyl ring modes

The bands observed at $1582, 1546\text{ cm}^{-1}$ in the IR spectrum $1586, 1546, 1482, 1262\text{ cm}^{-1}$ in the Raman spectrum and in the range $1587\text{--}1266\text{ cm}^{-1}$ theoretically (DFT) are assigned as phenyl ring stretching modes and these modes are expected in the region $1620\text{--}1250\text{ cm}^{-1}$ [65]. The ring breathing modes for the para di-substituted benzenes with entirely different substituent [70] have been reported in the interval $740\text{--}840\text{ cm}^{-1}$. For the title compound the ring breathing modes are observed at 824 cm^{-1} in Raman spectrum and assigned at 816 cm^{-1} theoretically (DFT). The ring-breathing mode of para-substituted benzenes were reported at 804 and 792 cm^{-1} experimentally and at 782 and 795 cm^{-1} theoretically [84, 85]. Aromatic compounds commonly exhibit multiple weak bands in the region $3100\text{--}3000\text{ cm}^{-1}$, due to aromatic CH stretching vibrations [65]. For the title compound the bands observed at $3056, 3024\text{ cm}^{-1}$ in the IR spectrum $3091, 3063, 3034\text{ cm}^{-1}$ in the Raman spectrum and the corresponding theoretical values (DFT) are $3091, 3081, 3064, 3029\text{ cm}^{-1}$. For para substituted benzenes, the in-plane C-H deformation modes are seen in the range $990\text{--}1315\text{ cm}^{-1}$ [65]. Band observed at 1230 cm^{-1} in the Raman spectrum is assigned as

C-H in-plane deformation modes for the ring Ph. The corresponding theoretical values (DFT) are 1234, 1158, 1153, 1086 cm^{-1} . The C-H out-of-plane deformations are observed between 1000 and 700 cm^{-1} [65]. For the title compound, γ C-H modes are observed at 902 cm^{-1} in IR spectrum and 911, 805, 795 cm^{-1} in Raman spectrum. The DFT calculations give γ C-H vibration at 929, 911, 804, 784 cm^{-1} .

In order to investigate the performance of vibrational wavenumbers of the title compound, the root mean square (RMS) value between the calculated and observed wavenumbers were calculated. The RMS values of wavenumbers were calculated using the following expression [86].

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

The RMS errors of the observed IR and Raman bands are found to be 6.49 and 6.72 for B3LYP/6-311++G (d, p) (5D, 7F) method.

4.3. NMR spectra

With TMS as internal standard experimental NMR spectral data (Figs. S4 and S5 supporting materials) of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide in DMSO are obtained at 300 MHz and is shown in Table 3. B3LYP/GIAO was used to calculate the absolute isotropic chemical shielding of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide [87] and numerical values of chemical shift $\delta_{pred} = \sigma_{calc}(\text{TMS}) - \sigma_{calc}$ together with calculated values of $\sigma_{calc}(\text{TMS})$, are reported in Table 3. The experimental data with peak positions of the titled compound is ^1H NMR (300 MHz, DMSO): δ 7.45(d, 2H, meta to -OH group); δ 6.85 (d, 2H, orho to OH group); δ 3.84 (t, 2H, N-CH₂-); δ 2.22 (s, 3H, -CH₃ at 4-position); δ 2.06 (s, 3H, -CH₃ at 5-position) δ 1.43 (m, 2H, CH₂-C₂H₅ of butyl group); δ 1.06 (m, 2H, CH₂-CH₃ of butyl group); δ 0.71 (t, 3H, CH₃ of butyl group): ^{13}C NMR (75 MHz, DMSO): 131.20(5- C), 124.16(meta C of OH), 119.84(para C of OH), 115.35(Orho C of OH), 31.59(CH₂-C₂H₅), 18.91(CH₂-CH₃ of butyl group), 13.20(butyl-CH₃), 8.53(4-CH₃), 7.39(5--CH₃). It is seen that chemical shift was in agreement with the experimental NMR data.

4.4. Frontier molecular orbitals

The frontier molecular orbitals can offer a reasonable qualitative prediction of the excitation properties and the ability of electron transport [88, 89]. The energies of the HOMO and LUMO orbitals of the title compound are calculated using B3LYP/6-311++G (d, p) (5D, 7F) basis set and shown in Fig. S6 (supporting material). The energies of HOMO and LUMO

are negative, which indicates that the studied compound is stable [90]. Using HOMO and LUMO orbital energies, the ionization energy and electron affinity can be expressed as: $I = -E_{\text{HOMO}}$, $A = -E_{\text{LUMO}}$, $\eta = (-E_{\text{HOMO}} + E_{\text{LUMO}})/2$ and $\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2$ [91]. Parr *et al.*, [92] proposed the global electrophilicity power of a ligand as $\omega = \mu^2/2\eta$. The hardness η and chemical potential μ are given by the following relations: $\eta = (I-A)/2$ and $\mu = -(I + A)/2$, where I and A are the first ionization potential and electron affinity of the chemical species [93]. For the title compound, $E_{\text{HOMO}} = -7.99$ eV, $E_{\text{LUMO}} = -5.11$ eV, Energy gap = $E_{\text{LUMO}} - E_{\text{HOMO}} = 2.88$ eV, Ionization potential $I = 6.43$ eV, Electron affinity $A = -0.1659$ eV, global hardness $\eta = 3.22$ eV, chemical potential $\mu = -3.21$ eV and global electrophilicity = $\mu^2/2\eta = 1.60$ eV.

4.5. Molecular Electrostatic Potential (MEP)

MEP is very useful descriptor in understanding sites for electrophilic attack and nucleophilic reactions and for the study of biological recognition process [94-96]. 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. Fig. S7 (supporting material) provides a visual presentation of the chemically active sites and comparative reactivity of atoms. Potential value increases in the order red < orange < yellow < green < blue. The negative (red and yellow) regions of MEP were related to electrophilic reactivity and the positive (blue) regions to nucleophilic reactivity. From the MEP of the title compound it is evident that the negative charge covers the N₁₄-O₂₄. The positive region is over the OH group.

4.6. ALIE surfaces, intra-molecular non-covalent interactions and Fukui functions

ALIE represents important theoretical tool for prediction of reactivity of organic molecules. This powerful quantum-molecular descriptor was introduced by Sjöberg *et al.* [97, 98] and it is defined as a sum of orbital energies weighted by the orbital densities:

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

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. After mapping of ALIE values to the electron density surface one visualizes molecule areas where the lowest energies are needed for the removal of electron. The areas with the lowest ALIE values are the ones where electrons are least tightly bound and they are most likely to be prone to electrophilic attacks. ALIE surface of the title molecule is presented in Fig.2.

ALIE surface indicates that the molecule area prone to electrophilic attacks is located in the near vicinity of oxygen atom O24. This is the location where electrons are least tightly bound, corresponding to ionization energy of 167 kcal/mol. On the other side blue colour indicates molecule sites where the highest amounts of energy are needed for the removal of electrons. According to the results presented in Fig.2 it can be seen that electrons are most tightly bound in the near vicinity of hydrogen atom H26, indicating this atom also as potential reactivity center.

Examination of electron density between atoms can indicate if there exist non-covalent interactions which generally influence the overall stability and structural properties of molecule. In this regard it is important to locate bond critical points, i.e. where electron density is minimal at some point along the line connecting two atoms, but is maximal in both directions perpendicular to the bond. Further, low density and reduced gradient values are characteristic for noncovalent interactions. These locations can be located by generation of gradient isosurfaces that enclose aforementioned regions of real space, while further insight into the interaction types can be understood by examination of values of $\text{sign}(\lambda_2)\rho$ in these regions. λ_2 is one of the three eigenvalues of the electron-density Hessian (second derivative) matrix, in agreement with the condition that $\nabla^2\rho = \lambda_1 + \lambda_2 + \lambda_3$ ($\lambda_1 \leq \lambda_2 \leq \lambda_3$). Thus, concerning the noncovalent interactions, analysis of sign of the λ_2 provides information whether the interactions are bonded ($\lambda_2 < 0$) or nonbonded ($\lambda_2 > 0$), while density provides information on the strength. Total of four intra-molecular non-covalent interactions have been detected. Aliphatic side chain is involved in three of them, while non-covalent interaction between oxygen atom O24 and hydrogen atom H10 turned out to be the strongest one, as indicated in Fig.3. In Fig.3 numerical values provided in red color present interaction strength expressed in terms of electron density, concretely in electrons/bohr³. Numeration of atoms has been presented by numerical values in black colour in Fig.3.

Changes concerning the molecule's electron density after addition or removal of charge are important indicators of its local reactivity. These changes can be described by the concept of Fukui functions which are in Jaguar calculated in finite difference approximation according to the 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 is number of electrons in the reference state of the molecule and δ represents the fraction of electron, which is set to be 0.01 [99]. By mapping the Fukui functions values to the electron density surface one obtains visualized locations where electron density changed the most, Fig.4.

Positive colour in case of Fukui f^+ function indicates the molecule locations where electron density increased with the addition of charge, while negative colour in case of Fukui f^- function indicates molecule location where electron density decreased with the removal of charge. In Fig.4 positive colour is purple, while negative colour is red. Results presented in Fig.4a show that purple colour is located in the near vicinity of carbon atoms C1 and C4, designating them as possible reaction centers in case of addition of charge. In the case of Fukui f^- function in Fig.4b, it can be seen that negative colour is located between atoms C6 and C11, meaning that electron density here decreased with the removal of charge.

4.7. Fukui indices

The Fukui function is a local reactivity descriptor that indicates the preferred regions where a chemical species will change its density when the number of electrons is modified and hence, it indicates the propensity of the electronic density to deform at a given position upon accepting or donating electrons [100-102]. Also, it is possible to define the corresponding condensed or atomic Fukui functions on the j^{th} atom site as,

$$f_j^- = q_j(N) - q_j(N-1)$$

$$f_j^+ = q_j(N+1) - q_j(N)$$

$$f_j^0 = \frac{1}{2}[q_j(N+1) - q_j(N-1)]$$

In these equations, q_j is the atomic charge (evaluated from Mulliken population analysis, electrostatic derived charge, etc.) at the j^{th} atomic site in the neutral (N), anionic ($N + 1$) or cationic ($N - 1$) chemical species. Chattaraj *et al.*, [103] have introduced the concept of generalized philicity which contains almost all information about hitherto known different global and local reactivity and selectivity descriptor, in addition to the information regarding electrophilic/nucleophilic power of a given atomic site in a molecule. Morell *et al.*, [104] have proposed a dual descriptor ($\Delta f(r)$), which is defined as the difference between the nucleophilic and electrophilic Fukui function and is given by, $\Delta f(r) = [f^+(r) - f^-(r)]$. When $\Delta f(r) > 0$, then the site is favoured for a nucleophilic attack while if $\Delta f(r) < 0$, then the site may be favoured for an electrophilic attack. The results are tabulated in Table 4.

4.8. Natural Bond Orbital Analysis

The natural bond orbitals (NBO) calculations were performed using NBO 3.1 program [105] as implemented in the Gaussian09 package at the DFT/B3LYP level and the

important results are given in tables 5 and 6. The various strong intra-molecular hyperconjugative interactions are: C₁₁-N₁₄ from N₁₅ of $n_1(N_{15}) \rightarrow \pi^*(C_{11}-N_{14})$, C₁₁-N₁₄ from O₃₇ of $n_1(O_{37}) \rightarrow \sigma^*(C_{11}-N_{14})$, C₁₁-N₁₄ from O₃₇ of $n_2(O_{37}) \rightarrow \sigma^*(C_{11}-N_{14})$, C₁₁-N₁₄ from O₃₇ of $n_3(O_{37}) \rightarrow \pi^*(C_{11}-N_{14})$, C₃-C₄ from O₃₈ of $n_1(O_{38}) \rightarrow \sigma^*(C_3-C_4)$, C₂-C₃ from O₃₈ of $n_2(O_{38}) \rightarrow \pi^*(C_2-C_3)$ with electron densities, 0.63126, 0.05087, 0.05087, 0.63126, 0.02733, 0.39695e and stabilization energies, 51.14, 5.23, 10.05, 55.46, 6.24, 27.89 kJ/mol.

The natural hybrid orbitals with higher energies, considerable p-character and low occupation numbers are $n_2(O_{37})$ and $n_2(O_{38})$ with energies, -0.20280 and -0.31149 a.u. and p-characters 99.96 and 100%) and low occupation numbers, 1.91090 and 1.87071 while the orbitals with lower energies and high occupation numbers are: $n_1(O_{37})$ and $n_1(O_{38})$ with energies, -0.72830, -0.58909 a.u. and with p-characters, 20.94, 55.27% and occupation numbers 1.98038 and 1.98033.

4.9. Nonlinear optical properties

The first hyperpolarizability (β_0) of this novel molecular system is calculated using B3LYP/6-311++G (d, p) (5D, 7F) method, based on the finite field approach [106]. The calculated first hyperpolarizability of the title compound is 3.61×10^{-30} esu, which is comparable with the reported values of similar derivatives [30] and which is 27.76 times that of standard NLO material urea (0.13×10^{-30} esu) [107]. The average second hyperpolarizability has been calculated by using the following expression,

$$\langle \gamma \rangle = (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz})/5.$$

The theoretical second order hyperpolarizability was calculated using the Gaussian09 software and is equal to $1.30020041 \times 10^{-36}$ esu [108-110].

4.10. Mulliken Charges

Mulliken charges are calculated by determining the electron population of each atom as defined in the basis functions and the charge distributions calculated by the Mulliken [111] and NBO methods for the equilibrium geometry of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide are given in Table 7. In 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide, the Mulliken atomic charge of the carbon atoms in the neighbourhood of C₃, C₁₁, C₁₂ and C₁₃ become more positive, shows the direction of delocalization and shows that the natural atomic charges are more sensitive to the changes in the molecular structure than Mulliken's net charges. The results are given in Fig.S8 (supporting material).

4.11. Degradation properties based on autoxidation and hydrolysis

Molecule locations possibly prone to the process of autoxidation can be initially determined by calculation of BDE. Taking into account that rate in autoxidation process is related to the abstraction of hydrogen atom from the parent drug molecule by peroxy radical [112, 113], it can be concluded that if the BDE of hydrogen abstraction is in the certain energy interval, then location of that hydrogen atom is a candidate for the start of autoxidation. All peroxy radicals have similar BDE values (in the range of 87 kcal/mol to 92 kcal/mol) and these values are almost completely independent of the chemical surrounding [112, 114]. According to the study of Wright et al. [115], range of BDE values from 75 kcal/mol to 85 kcal/mol indicate the highest risk for some molecule to be subjected to autoxidation [112, 115], while BDE values below 70–75 kcal/mol are not appropriate for the degradation by autoxidation. In this work BDEs of all single acyclic bonds have been presented in Fig.5, where values for hydrogen abstraction are given in red color, while values for the rest of the single acyclic bonds are given in blue colour.

According to the BDE values there are two locations with BDE values suitable to be considered as candidates for the start of autoxidation. These locations are OH group and methyl group at imidazolium ring (bonds denoted with numbers 4 and 5). BDE for hydrogen abstraction at OH group is below 85 kcal/mol, indicating this location as the most sensitive towards the autoxidation. BDE values of the rest of the single acyclic bonds indicate very interesting situation in the case of bond denoted with number 14. Namely, in this case calculated BDE was ~47 kcal/mol, clearly indicating that this bond is the easiest to break, thus being important for the process of degradation. This bond connects aliphatic side chain and as we move to the end of this chain the BDE values of bonds increase. Very low BDE value in the case of bond 14 could be due to the higher electro-negativity of nitrogen atom and involvement of aliphatic side chain in three non-covalent interactions, which weakens the mentioned bond.

In this work we have also determined which atoms of title molecule have pronounced interactions with water molecules by calculation of RDFs obtained after MD simulations. RDF, $g(r)$, is probability of finding a particle in the distance r from another particle [116] and its curve profile and peak distance indicate how much meaningful are interactions with water molecules. RDFs of atoms with significant interactions are presented in Fig.6.

Calculated RDFs indicate that among carbon atoms the most significant interactions with water molecules are having C16 and C36, with the highest $g(r)$ values of almost 1.4 and peak distance at around 4.5 Å. Other carbon atoms with relatively significant interactions with water molecules are atoms C2, C4, C20 and C33. Much more interesting situation,

regarding interactions with water, happened in the case of non-carbon atoms. The most important interactions with water molecules has hydrogen atom H26, with the highest $g(r)$ value of somewhat higher than 1.4 and with peak distance at around 1.6 Å. Other two atoms with significant interactions are oxygen atoms O24 and O25. Both of these atoms have peak distance at around 2.5 Å, while the highest $g(r)$ value of O24 is much higher and has the value of almost 1.9. Other non-carbon atoms with significant interactions with water molecules are hydrogen atoms H8 and H9, and nitrogen atom N14.

4.12. Molecular Docking

Imidazole and its derivatives are physiologically and pharmacologically active and used as treatment of several diseases. Many imidazoles are reported as pharmacological agents like Azomycine, Clotrimazole, Miconazole, Ergothionine, Mlonidine and Moxonidine. One of the most important applications of imidazole derivatives are used as a material for treatment of cancer [19]. Baroniya *et al.*, [117] reported certain imidazole derivatives shows activity against cancer. Sharma *et al.*, [118] reported synthesized imidazole derivative shows anticancer activity. High resolution crystal structure of CDK inhibitor was downloaded from the RSCB protein data bank website (PDB ID: 2XMY) and all molecular docking calculations were performed on Auto Dock-Vina software [119, 120] and as reported in literature [79]. Using Discover Studio Visualizer 4.0 software the ligand-substrate interactions are analyzed (Figs. S9 and S10 – supporting material) and the non-covalent interactions are as given below; sAla95, Met91, Arg199 amino acids form alkyl interaction with CH₃ moiety. Asp92, Glu195 amino acids forms π -anion interaction with imidazole and phenyl ring. Lys88 amino acid forms π -cation interaction with phenyl ring. Amino acids Tyr88, Lys88 forms H-bond interaction with OH and NO group. The docked ligand title compound forms a stable complex with CDK inhibitor and gives a binding affinity (ΔG in kcal/mol) value of -6.3 (table 8). These preliminary results suggest that the compound might exhibit inhibitory activity against CDK inhibitor (Fig.7).

5. Conclusion

The FT-IR and FT-Raman studies of the title compound in the ground state were reported experimentally and theoretically. Potential energy distribution of normal modes of vibrations was done using GAR2PED program. The ring stretching modes in IR and Raman spectra are evidence for charge transfer interaction between the donor and the acceptor group through the π system. The chemical reactivity is understood from chemical potential, electrophilicity and global hardness. MEP predicts the most reactive part in the molecule.

Optimized geometrical parameters of the title compound are in agreement with that of similar derivatives. The calculated first hyperpolarizability is comparable with the reported values of similar derivatives and the study of second hyperpolarizability reveals it as an attractive compound for future studies in nonlinear optics. The calculated NMR results are in good agreement with experimental data. ALIE surfaces show that electrons are least tightly bound in the near vicinity of oxygen atom O24, indicating this location to be prone to electrophilic attacks. Analysis of intra-molecular non-covalent interactions shows that there are four such interactions, with aliphatic chain being involved in three of them. According to the Fukui functions possible important reactions centers include carbon atoms C1, C4, C6 and C11. BDE values of hydrogen abstraction indicate two possible locations for the start of autoxidation process, hydrogen atoms of OH and one methyl groups, with significantly lower BDE value (84 kcal/mol) in the case of hydrogen atom belonging to the OH group. Additionally, the lowest BDE value was calculated for the bond that connects aliphatic side chain with imidazolium ring, indicating this position as interesting for the process of degradation. RDFs show that five carbon and six non-carbon atoms are having pronounced interactions with water molecules. Among these the most important RDFs are for the atoms H26, O24 and O25. Of these, the lowest peak distance, around 1.6Å, was calculated for the hydrogen atom H26, while the highest $g(r)$ value, around 1.9, was calculated for the oxygen atom O24. The molecular docking results suggest that the title compound might exhibit inhibitory activity against CDK inhibitor

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Figure Captions

Fig.1 Optimized geometry of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide

Fig. 2 ALIE surface of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide molecule

Fig. 3 Intra-molecular non-covalent interactions of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide molecule

Fig. 4 Fukui functions of title molecule a) f^+ and b) f^- functions

Fig. 5. BDE of all single acyclic bonds of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide molecule

Fig.6 RDFs of a) carbon and b) non-carbon atoms with significant interactions with water

Fig.7 Surface view of receptor with docked ligand embedded in the active site.

Table 1. Optimized geometrical parameters of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide

Bond lengths(Å)

C ₁ -C ₂	1.389	C ₁ -C ₆	1.406	C ₁ -H ₇	1.082
C ₂ -C ₃	1.394	C ₂ -H ₈	1.083	C ₃ -C ₄	1.396
C ₃ -O ₂₅	1.368	C ₄ -C ₅	1.389	C ₄ -H ₉	1.086
C ₅ -C ₆	1.407	C ₅ -H ₁₀	1.081	C ₆ -C ₁₁	1.458
C ₁₁ -N ₁₄	1.354	C ₁₁ -N ₁₅	1.383	C ₁₂ -C ₁₃	1.370
C ₁₂ -N ₁₅	1.388	C ₁₂ -C ₂₀	1.493	C ₁₃ -N ₁₄	1.394
C ₁₃ -C ₁₆	1.486	N ₁₄ -O ₂₄	1.297	N ₁₅ -C ₂₇	1.465
C ₁₆ -H ₁₇	1.094	C ₁₆ -H ₁₈	1.094	C ₁₆ -H ₁₉	1.091
C ₂₀ -H ₂₁	1.090	C ₂₀ -H ₂₂	1.095	C ₂₀ -H ₂₃	1.094
O ₂₅ -H ₂₆	0.963	C ₂₇ -H ₂₈	1.090	C ₂₇ -H ₂₉	1.092
C ₂₇ -C ₃₀	1.536	C ₃₀ -H ₃₁	1.095	C ₃₀ -H ₃₂	1.094
C ₃₀ -C ₃₃	1.537	C ₃₃ -H ₃₄	1.097	C ₃₃ -H ₃₅	1.095
C ₃₃ -C ₃₆	1.534	C ₃₆ -H ₃₇	1.093	C ₃₆ -H ₃₈	1.095
C ₃₆ -H ₃₉	1.094				

Bond angles(°)

C ₂ -C ₁ -C ₆	121.5	C ₂ -C ₁ -H ₇	118.2	C ₆ -C ₁ -H ₇	120.3
C ₁ -C ₂ -C ₃	119.8	C ₁ -C ₂ -H ₈	121.0	C ₃ -C ₂ -H ₈	119.2
C ₂ -C ₃ -C ₄	119.6	C ₂ -C ₃ -O ₂₅	117.6	C ₄ -C ₃ -O ₂₅	122.8
C ₃ -C ₄ -C ₅	120.4	C ₃ -C ₄ -H ₉	120.0	C ₅ -C ₄ -H ₉	119.6
C ₄ -C ₅ -C ₆	120.9	C ₄ -C ₅ -H ₁₀	120.1	C ₆ -C ₅ -H ₁₀	118.9
C ₁ -C ₆ -C ₅	117.7	C ₁ -C ₆ -C ₁₁	122.7	C ₅ -C ₆ -C ₁₁	119.5
C ₆ -C ₁₁ -N ₁₄	124.5	C ₆ -C ₁₁ -N ₁₅	128.4	N ₁₄ -C ₁₁ -N ₁₅	107.1
C ₁₃ -C ₁₂ -N ₁₅	107.4	C ₁₃ -C ₁₂ -C ₂₀	129.2	N ₁₅ -C ₁₂ -C ₂₀	123.4
C ₁₂ -C ₁₃ -N ₁₄	107.4	C ₁₂ -C ₁₃ -C ₁₆	133.0	N ₁₄ -C ₁₃ -C ₁₆	119.6
C ₁₁ -N ₁₄ -C ₁₃	109.3	C ₁₁ -N ₁₄ -O ₂₄	127.1	C ₁₃ -N ₁₄ -O ₂₄	123.4

C ₁₁ -N ₁₅ -C ₁₂	108.8	C ₁₁ -N ₁₅ -C ₂₇	125.8	C ₁₂ -N ₁₅ -C ₂₇	124.3
C ₁₃ -C ₁₆ -H ₁₇	110.5	C ₁₃ -C ₁₆ -H ₁₈	110.7	C ₁₃ -C ₁₆ -H ₁₉	111.0
H ₁₇ -C ₁₆ -H ₁₈	106.6	H ₁₇ -C ₁₆ -H ₁₉	108.9	H ₁₈ -C ₁₆ -H ₁₉	108.9
C ₁₂ -C ₂₀ -H ₂₁	109.5	C ₁₂ -C ₂₀ -H ₂₂	112.2	C ₁₂ -C ₂₀ -H ₂₃	112.5
H ₂₁ -C ₂₀ -H ₂₂	107.3	H ₂₁ -C ₂₀ -H ₂₃	107.5	H ₂₂ -C ₂₀ -H ₂₃	107.5
C ₃ -O ₂₅ -H ₂₆	109.7	N ₁₅ -C ₂₇ -H ₂₈	107.5	N ₁₅ -C ₂₇ -H ₂₉	107.6
N ₁₅ -C ₂₇ -C ₃₀	114.0	H ₂₈ -C ₂₇ -H ₂₉	106.7	H ₂₈ -C ₂₇ -C ₃₀	110.2
H ₂₉ -C ₂₇ -C ₃₀	110.4	C ₂₇ -C ₃₀ -H ₃₁	109.6	C ₂₇ -C ₃₀ -H ₃₂	108.8
C ₂₇ -C ₃₀ -C ₃₃	113.2	H ₃₁ -C ₃₀ -H ₃₂	106.1	H ₃₁ -C ₃₀ -C ₃₃	109.5
H ₃₂ -C ₃₀ -C ₃₃	109.4	C ₃₀ -C ₃₃ -H ₃₄	109.2	C ₃₀ -C ₃₃ -H ₃₅	108.1
C ₃₀ -C ₃₃ -C ₃₆	114.6	H ₃₄ -C ₃₃ -H ₃₅	105.9	H ₃₄ -C ₃₃ -C ₃₆	109.5
H ₃₅ -C ₃₃ -C ₃₆	108.9	C ₃₃ -C ₃₆ -H ₃₇	110.8	C ₃₃ -C ₃₆ -H ₃₈	111.1
C ₃₃ -C ₃₆ -H ₃₉	112.2	H ₃₇ -C ₃₆ -H ₃₈	107.6	H ₃₇ -C ₃₆ -H ₃₉	107.2
H ₃₈ -C ₃₆ -H ₃₉	107.7				
<u>Dihedral angles(°)</u>					
C ₆ -C ₁ -C ₂ -C ₃	0.9	C ₆ -C ₁ -C ₂ -H ₈	179.5	H ₇ -C ₁ -C ₂ -C ₃	-177.2
H ₇ -C ₁ -C ₂ -H ₈	1.5	C ₂ -C ₁ -C ₆ -C ₅	-1.9	C ₂ -C ₁ -C ₆ -C ₁₁	179.6
H ₇ -C ₁ -C ₆ -C ₅	176.2	H ₇ -C ₁ -C ₆ -C ₁₁	-2.3	C ₁ -C ₂ -C ₃ -C ₄	0.5
C ₁ -C ₂ -C ₃ -O ₂₅	179.8	H ₈ -C ₂ -C ₃ -C ₄	-178.2	H ₈ -C ₂ -C ₃ -O ₂₅	1.1
C ₂ -C ₃ -C ₄ -C ₅	-0.7	C ₂ -C ₃ -C ₄ -H ₉	178.8	O ₂₅ -C ₃ -C ₄ -C ₅	179.9
O ₂₅ -C ₃ -C ₄ -H ₉	-0.4	C ₂ -C ₃ -O ₂₅ -H ₂₆	-178.2	C ₄ -C ₃ -O ₂₅ -H ₂₆	1.0
C ₃ -C ₄ -C ₅ -C ₆	-0.4	C ₃ -C ₄ -C ₅ -H ₁₀	177.7	H ₉ -C ₄ -C ₅ -C ₆	-179.9
H ₉ -C ₄ -C ₅ -H ₁₀	-1.8	C ₄ -C ₅ -C ₆ -C ₁	1.7	C ₄ -C ₅ -C ₆ -C ₁₁	-179.8
H ₁₀ -C ₅ -C ₆ -C ₁	-176.5	H ₁₀ -C ₅ -C ₆ -C ₁₁	2.0	C ₁ -C ₆ -C ₁₁ -N ₁₄	145.5
C ₁ -C ₆ -C ₁₁ -N ₁₅	-35.5	C ₅ -C ₆ -C ₁₁ -N ₁₄	-32.9	C ₅ -C ₆ -C ₁₁ -N ₁₅	146.1
C ₆ -C ₁₁ -N ₁₄ -C ₁₃	179.8	C ₆ -C ₁₁ -N ₁₄ -O ₂₄	-1.2	N ₁₅ -C ₁₁ -N ₁₄ -C ₁₃	0.6
N ₁₅ -C ₁₁ -N ₁₄ -O ₂₄	179.6	C ₆ -C ₁₁ -N ₁₅ -C ₁₂	-179.0	C ₆ -C ₁₁ -N ₁₅ -C ₂₇	-10.0
N ₁₄ -C ₁₁ -N ₁₅ -C ₁₂	-0.1	N ₁₄ -C ₁₁ -N ₁₅ -C ₂₇	169.0	N ₁₅ -C ₁₂ -C ₁₃ -N ₁₄	0.8

N ₁₅ -C ₁₂ -C ₁₃ -C ₁₆	-178.6	C ₂₀ -C ₁₂ -C ₁₃ -N ₁₄	-177.7	C ₂₀ -C ₁₂ -C ₁₃ -C ₁₆	3.0
C ₁₃ -C ₁₂ -N ₁₅ -C ₁₁	-0.5	C ₁₃ -C ₁₂ -N ₁₅ -C ₂₇	-169.8	C ₂₀ -C ₁₂ -N ₁₅ -C ₁₁	178.1
C ₂₀ -C ₁₂ -N ₁₅ -C ₂₇	8.7	C ₁₃ -C ₁₂ -C ₂₀ -H ₂₁	3.9	C ₁₃ -C ₁₂ -C ₂₀ -H ₂₂	122.9
C ₁₃ -C ₁₂ -C ₂₀ -H ₂₃	-115.6	N ₁₅ -C ₁₂ -C ₂₀ -H ₂₁	-174.3	N ₁₅ -C ₁₂ -C ₂₀ -H ₂₂	-55.3
N ₁₅ -C ₁₂ -C ₂₀ -H ₂₃	66.2	C ₁₂ -C ₁₃ -N ₁₄ -C ₁₁	-0.9	C ₁₂ -C ₁₃ -N ₁₄ -O ₂₄	-180.0
C ₁₆ -C ₁₃ -N ₁₄ -C ₁₁	178.6	C ₁₆ -C ₁₃ -N ₁₄ -O ₂₄	-0.5	C ₁₂ -C ₁₃ -C ₁₆ -H ₁₇	121.0
C ₁₂ -C ₁₃ -C ₁₆ -H ₁₈	-121.0	C ₁₂ -C ₁₃ -C ₁₆ -H ₁₉	0.1	N ₁₄ -C ₁₃ -C ₁₆ -H ₁₇	-58.2
N ₁₄ -C ₁₃ -C ₁₆ -H ₁₈	59.6	N ₁₄ -C ₁₃ -C ₁₆ -H ₁₉	-179.1	C ₁₁ -N ₁₅ -C ₂₇ -H ₂₈	-13.9
C ₁₁ -N ₁₅ -C ₂₇ -H ₂₉	-128.6	C ₁₁ -N ₁₅ -C ₂₇ -C ₃₀	108.5	C ₁₂ -N ₁₅ -C ₂₇ -H ₂₈	153.6
C ₁₂ -N ₁₅ -C ₂₇ -H ₂₉	38.9	C ₁₂ -N ₁₅ -C ₂₇ -C ₃₀	-83.9	N ₁₅ -C ₂₇ -C ₃₀ -H ₃₁	63.9
N ₁₅ -C ₂₇ -C ₃₀ -H ₃₂	-51.6	N ₁₅ -C ₂₇ -C ₃₀ -C ₃₃	-173.5	H ₂₈ -C ₂₇ -C ₃₀ -H ₃₁	-175.1
H ₂₈ -C ₂₇ -C ₃₀ -H ₃₂	69.3	H ₂₈ -C ₂₇ -C ₃₀ -C ₃₃	-52.6	H ₂₉ -C ₂₇ -C ₃₀ -H ₃₁	-57.4
H ₂₉ -C ₂₇ -C ₃₀ -H ₃₂	-173.0	H ₂₉ -C ₂₇ -C ₃₀ -C ₃₃	65.1	C ₂₇ -C ₃₀ -C ₃₃ -H ₃₄	57.1
C ₂₇ -C ₃₀ -C ₃₃ -H ₃₅	172.1	C ₂₇ -C ₃₀ -C ₃₃ -C ₃₆	-66.2	H ₃₁ -C ₃₀ -C ₃₃ -H ₃₄	179.8
H ₃₁ -C ₃₀ -C ₃₃ -H ₃₅	-65.3	H ₃₁ -C ₃₀ -C ₃₃ -C ₃₆	56.4	H ₃₂ -C ₃₀ -C ₃₃ -H ₃₄	-64.4
H ₃₂ -C ₃₀ -C ₃₃ -H ₃₅	50.5	H ₃₂ -C ₃₀ -C ₃₃ -C ₃₆	172.2	C ₃₀ -C ₃₃ -C ₃₆ -H ₃₇	-176.1
C ₃₀ -C ₃₃ -C ₃₆ -H ₃₈	-56.6	C ₃₀ -C ₃₃ -C ₃₆ -H ₃₉	64.0	H ₃₄ -C ₃₃ -C ₃₆ -H ₃₇	60.6
H ₃₄ -C ₃₃ -C ₃₆ -H ₃₈	-179.8	H ₃₄ -C ₃₃ -C ₃₆ -H ₃₉	-59.1	H ₃₅ -C ₃₃ -C ₃₆ -H ₃₇	-54.9
H ₃₅ -C ₃₃ -C ₃₆ -H ₃₈	64.6	H ₃₅ -C ₃₃ -C ₃₆ -H ₃₉	-174.6		

Table 2. IR, Raman bands and calculated (scaled) wavenumbers of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide and assignments.

B3LYP/6-31++G(d,p)(5D,7F)IR			Raman		Assignments ^a
$\nu(\text{cm}^{-1})$ IR _I	R_A		$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3685	92.13	180.49	3665	-	$\nu\text{OH}(100)$
3091	3.22	37.66	-	3091	$\nu\text{CH}(98)$
3081	5.50	110.24	-	-	$\nu\text{CH}(100)$
3064	6.26	94.60	3056	3063	$\nu\text{CH}(99)$
3029	22.03	153.54	3024	3034	$\nu\text{CH}(98)$
3001	13.90	93.49	-	-	$\nu\text{Me}(89)$
2995	14.47	46.36	-	2994	$\nu\text{Me}(97)$
2991	12.43	14.31	-	-	$\nu\text{CH}_2(92)$
2971	48.11	67.36	-	2970	$\nu\text{Me}(93)$
2965	44.62	64.98	-	-	$\nu\text{Me}(89)$
2963	9.48	94.41	2959	-	$\nu\text{Me}(100)$
2949	49.33	51.85	-	-	$\nu\text{CH}_2(96)$
2944	23.99	113.91	-	-	$\nu\text{Me}(81), \nu\text{CH}_2(12)$
2939	6.23	82.28	-	2935	$\nu\text{CH}_2(53), \nu\text{Me}(45)$
2931	16.26	161.29	2928	-	$\nu\text{CH}_2(59), \nu\text{Me}(40)$
2917	31.40	306.05	-	-	$\nu\text{Me}(99)$
2913	6.61	150.25	-	-	$\nu\text{CH}_2(91)$
2906	24.33	91.79	-	2908	$\nu\text{Me}(96)$
2902	42.76	256.36	-	-	$\nu\text{Me}(97)$
2897	15.33	125.72	2869	-	$\nu\text{CH}_2(93)$
1606	15.36	56.17	1606	1604	$\nu\text{C}=\text{C}(59), \nu\text{CC}(18)$
1587	72.75	499.13	1582	1586	$\nu\text{Ph}(49), \delta\text{Ph}(11), \delta\text{CH}(11)$
1558	6.86	43.53	1546	1546	$\nu\text{Ph}(66)$
1496	155.89	450.60	-	1482	$\nu\text{Ph}(41), \nu\text{CC}(37), \delta\text{CH}(16)$
1454	16.90	5.97	1453	1460	$\delta\text{CH}_2(83)$
1451	12.28	1.98	-	-	$\delta\text{Me}(71), \delta\text{CH}_2(13)$
1449	16.39	3.62	-	-	$\delta\text{Me}(58), \delta\text{CH}_2(40)$
1441	7.41	24.53	-	1443	$\delta\text{Me}(56), \delta\text{CH}_2(42))$
1437	1.39	28.18	-	-	$\delta\text{Me}(50), \delta\text{CH}_2(12), \nu\text{CN}(11)$
1434	0.71	23.86	-	-	$\delta\text{CH}_2(45), \delta\text{Me}(54)$

1432	4.16	31.23	-	-	$\delta\text{CH}_2(49)$, $\delta\text{Me}(46)$
1425	31.19	370.85	-	-	$\nu\text{C}=\text{N}(46)$, $\delta\text{Me}(49)$
1424	13.79	31.08	-	-	$\delta\text{Me}(32)$, $\nu\text{Ph}(22)$
1422	5.46	179.67	-	-	$\nu\text{Ph}(45)$, $\delta\text{Me}(43)$
1407	5.92	8.10	1402	1411	$\delta\text{Me}(97)$
1395	36.01	149.46	1385	1385	$\nu\text{CC}(41)$, $\nu\text{CN}(30)$
1375	3.36	13.29	-	-	$\delta\text{Me}(57)$, $\nu\text{CN}(19)$
1367	3.69	35.41	-	1363	$\delta\text{CH}_2(38)$, $\delta\text{Me}(41)$
1364	7.24	10.55	-	-	$\nu\text{CC}(52)$, $\delta\text{Me}(46)$
1361	2.67	11.26	-	-	$\delta\text{CH}_2(42)$, $\delta\text{Me}(43)$
1346	11.83	5.63	1341	-	$\nu\text{CN}(60)$, $\delta\text{CH}_2(32)$
1325	0.27	3.27	-	1334	$\delta\text{CH}_2(51)$, $\nu\text{CC}(47)$
1316	63.14	1726	-	-	$\delta\text{OH}(48)$, $\nu\text{Ph}(44)$
1305	92.69	33.00	-	-	$\nu\text{NO}(50)$, $\nu\text{CN}(45)$
1298	104.59	14.58	-	1292	$\nu\text{CN}(58)$, $\delta\text{CH}_2(36)$
1287	32.48	12.06	1283	1281	$\delta\text{CH}_2(44)$, $\nu\text{CC}(40)$, $\delta\text{Ring}(10)$
1266	1.67	9.53	-	1262	$\delta\text{CH}_2(47)$, $\nu\text{Ph}(31)$
1242	2.80	4.16	1246	1243	$\delta\text{CH}_2(69)$
1234	110.32	4.60	-	1230	$\nu\text{CO}(48)$, $\delta\text{CH}(40)$
1225	31.54	16.81	1211	1215	$\delta\text{CH}_2(65)$, $\nu\text{CO}(10)$
1174	3.47	20.80	1171	1171	$\delta\text{CH}_2(19)$, $\nu\text{CN}(46)$
1158	15.38	44.70	-	-	$\delta\text{CH}(61)$, $\nu\text{C}=\text{N}(10)$
1153	13.27	13.07	-	-	$\delta\text{CH}(47)$, $\nu\text{CN}(43)$
1143	221.19	8.21	-	1146	$\delta\text{OH}(28)$, $\nu\text{Ph}(21)$, $\delta\text{CH}(11)$
1115	16.18	25.44	1100	1125	$\delta\text{CH}_2(49)$, $\delta\text{Me}(10)$, $\nu\text{CN}(10)$
1086	20.48	1.62	-	-	$\delta\text{CH}(62)$, $\nu\text{Ph}(20)$
1080	15.80	15.47	-	1078	$\delta\text{Me}(52)$, $\nu\text{CC}(37)$
1075	0.69	12.95	1069	-	$\delta\text{Me}(52)$, $\nu\text{CC}(44)$
1050	3.36	37.11	-	1056	$\delta\text{OH}(21)$, $\nu\text{CN}(21)$
1031	1.28	3.88	-	1030	$\nu\text{CC}(90)$
1024	0.03	0.01	1021	-	$\delta\text{Me}(86)$
1012	1.09	0.12	-	-	$\delta\text{Me}(87)$
988	0.26	4.59	979	970	$\delta\text{Ph}(49)$, $\nu\text{Ph}(36)$
943	0.47	6.62	-	-	$\delta\text{Me}(51)$, $\nu\text{CC}(41)$

936	2.75	36.75	-	937	δ Me(45), ν CN(12)
929	1.27	4.23	-	-	γ CH(48), τ Me(37)
928	0.45	4.66	-	-	δ Me(39), δ CH ₂ (32)
911	0.12	0.53	902	911	γ CH(74), τ Ph(16)
884	1.25	1.70	880	888	ν CC(39), ν CN(28), δ Me(17)
844	0.93	16.54	838	851	ν CC(65), δ Me(10)
816	21.69	33.84	-	824	ν Ph(42), δ Me(16), ν CO(13)
804	41.42	1.87	-	805	γ CH(65), γ CO(12), τ Ph(10)
784	5.41	3.22	-	795	γ CH(91)
776	9.54	16.63	778	776	ν CC(53), δ CH ₂ (36)
753	7.04	4.47	751	743	δ CH ₂ (77), δ Me(16)
725	11.14	1.92	729	727	δ CH ₂ (69), δ Me(10)
699	0.39	2.76	-	692	τ PhI(59), γ CO(13), γ CC(13)
660	0.02	1.87	665	670	τ Ring(42), γ NO(25), γ CC(15)
656	6.03	6.11	-	-	τ Ring(13), δ CH ₂ (10)
634	1.08	7.61	641	633	τ Ring(23), δ Ph(22)
616	1.59	3.50	-	617	δ Ph(46), δ CC(25), δ NO(10)
604	5.99	1.94	595	594	τ Ring(52), γ CC(15)
578	19.59	2.43	-	-	δ Ph(48), δ Ring(12)
562	10.33	7.55	-	553	δ Ring(52), γ CC(18)
504	18.97	0.03	500	-	γ CO(33), τ Ph(31), γ CC(21)
421	6.87	3.75	425	420	δ CO(32), δ CC(16), δ Ph(13)
405	0.71	3.57	-	-	δ Ph(77)
402	2.61	2.15	-	394	δ CH ₂ (50), τ Ph(10)
379	9.57	4.76	-	382	δ CO(17), γ CC(26), τ Ph(13)
358	4.63	1.29	-	-	δ CN(24), δ NO(20)
341	8.77	4.65	-	345	δ CH ₂ (27), γ CN(18), γ CC(13), γ NO(11)
329	2.79	3.28	-	328	δ CC(19), τ CN(20), τ Ph(19)
313	103.59	1.54	-	315	τ CO(89)
298	4.24	0.63	-	286	δ CC(32), δ CN(18), τ CN(14)
279	3.28	0.74	-	-	δ CC(22), τ Me(17), δ CH ₂ (10)
275	1.83	0.46	-	265	δ CC(36), τ Me(16)
248	1.52	4.66	-	-	γ CC(47), τ Ph(27)
241	1.68	2.39	-	-	δ Ph(52), δ CC(14), γ CC(12)

226	0.62	0.83	-	216	δ CC(20), τ Ring(15), δ CH ₂ (14)
202	0.12	0.57	-	-	τ Me(36), δ CH ₂ (25)
170	0.56	0.54	-	175	τ Ph(25), δ CC(14), γ CC(10)
158	2.81	0.68	-	169	τ Ring(25), τ Me(14), γ CC(18)
134	0.59	0.66	-	133	τ CN(25), τ Me(15), τ Ph(10)
110	0.30	0.16	-	-	τ Me(53), τ CH ₂ (14), τ Ph(13)
97	1.45	0.09	-	-	τ Me(30), δ CC(14), τ Ph(15)
92	0.74	1.27	-	-	τ Me(63), τ Ph(17)
73	0.49	0.41	-	-	τ CH ₂ (32), τ CN(20), τ Me(23)
62	0.25	3.70	-	-	τ CC(45), γ CN(17), τ Ph(12)
50	4.14	5.24	-	-	τ CC(55), γ CC(18), τ Ph(10)
30	0.95	1.94	-	-	τ CN(38), γ CN(30), γ CC(11)
29	0.04	1.63	-	-	τ CH ₂ (65), τ Ph(21)

^a ν -stretching; δ -in-plane bending; γ -out-of-plane deformation; τ - torsion; Ph- phenyl ring; Ring-imidazole ring; Me-methyl; IR_I-IR intensity; R_A- Raman activity; potential energy distribution is given in brackets in the assignment column.

Table 3. Calculated ^1H and ^{13}C NMR parameters (with respect to TMS).

Label	σ_{TMS}	B3LYP/6-311++G	$\delta_{\text{calc}} = \sigma_{\text{TMS}} - \sigma_{\text{calc}}$
H ₇	32.7711	24.7152	8.0559
H ₈		24.8257	7.9454
H ₉		25.1921	7.5790
H ₁₀		24.6261	8.1450
H ₁₇		29.6917	3.0794
H ₁₈		29.6572	3.1139
H ₁₉		30.2182	2.5529
H ₂₁		29.9005	2.8706
H ₂₂		29.8483	2.9228
H ₂₃		29.9549	2.8162
H ₂₆		29.9125	2.8586
H ₂₈		28.8900	3.8811
H ₂₉		28.8097	3.9614
H ₃₁		31.0086	1.7625
H ₃₂		30.9788	1.7923
H ₃₄		31.3860	1.3851
H ₃₅		31.5844	1.1867
H ₃₇		31.9358	0.8353
H ₃₈		31.9046	0.8665
H ₃₉		31.8931	0.878
C1	189.6900	51.0556	138.6344
C2		65.1295	124.5605
C3		20.1531	169.5369
C4		65.7159	123.9741
C5		44.9084	144.7816
C6		59.0605	130.6295
C11		42.2763	147.4137
C12		59.5624	130.1276

C13	47.8646	141.8254
C16	173.763	15.927
C20	173.346	16.344
C27	135.664	54.026
C30	147.611	42.079
C33	158.532	31.158
<u>C36</u>	<u>169.449</u>	<u>20.241</u>

Table 4. Values of the Fukui functions considering Mulliken charges

Atoms	f_i^-	f_i^+	$\Delta f(r)$
C ₁	0.036288	0.018936	-0.01735
C ₂	0.005219	0.019692	0.014473
C ₃	0.0642	0.027791	-0.03641
C ₄	0.01471	0.017528	0.002818
C ₅	0.021724	0.013155	-0.00857
C ₆	0.020623	0.007922	-0.0127
H ₇	0.060932	0.043507	-0.01743
H ₈	0.07156	0.057873	-0.01369
H ₉	0.072553	0.05565	-0.0169
H ₁₀	0.050079	0.019216	-0.03086
C ₁₁	0.068125	0.089945	0.02182
C ₁₂	0.03238	0.037031	0.004651
C ₁₃	0.002244	0.007474	0.00523
N ₁₄	0.012704	-0.01985	-0.03256
N ₁₅	0.011328	0.002796	-0.00853
C ₁₆	-0.001622	-0.00775	-0.00613
H ₁₇	0.030927	0.029207	-0.00172
H ₁₈	0.029088	0.028081	-0.00101
H ₁₉	0.034657	0.044423	0.009766
C ₂₀	-0.007054	-0.00779	-0.00074
H ₂₁	0.035681	0.032424	-0.00326
H ₂₂	0.0423	0.039573	-0.00273
H ₂₃	0.044412	0.04118	-0.00323
O ₂₄	0.076035	0.229157	0.153122
O ₂₅	0.041411	0.050887	0.009476
H ₂₆	0.034352	0.02887	-0.00548
C ₂₇	-0.023409	-0.02448	-0.00107
H ₂₈	0.012148	0.018652	0.006504
H ₂₉	0.037803	0.035372	-0.00243

C ₃₀	-0.016749	-0.01492	0.001832
H ₃₁	0.038478	0.03572	-0.00276
H ₃₂	-0.000131	0.002219	0.00235
C ₃₃	-0.012787	-0.01071	0.002077
H ₃₄	0.019486	0.017215	-0.00227
H ₃₅	-0.006123	-0.0108	-0.00468
C ₃₆	-0.004504	-0.00366	0.000848
H ₃₇	0.025849	0.023146	-0.0027
H ₃₈	0.018138	0.018394	0.000256
H ₃₉	0.006946	0.006911	-0.000035

Table 5. Second-order perturbation theory analysis of Fock matrix in NBO basis corresponding to the intra molecular bonds of the title compound.

Donor (i)	Type	ED/e	Acceptor (j)	Type	ED/e	E(2) ^a (kJmol ⁻¹)	E(j)-E(i) ^b (a.u.)	F(i,j) ^c (a.u.)
C ₂ -C ₃	π	1.62754	C ₁ -C ₆	π^*	0.42501	23.62	0.28	0.074
-	-		C ₂ -C ₃	π^*	0.39695	0.69	0.28	0.013
-	-		C ₄ -C ₅	π^*	0.31858	16.55	0.29	0.063
C ₃ -C ₄	σ	1.98132	C ₂ -C ₃	σ^*	0.02502	3.60	1.27	0.060
-	-		C ₄ -C ₅	σ^*	0.01477	2.75	1.30	0.053
C ₁₁ -N ₁₄	σ	1.98202	C ₁ -C ₆	σ^*	0.02320	1.57	1.39	0.042
-	-		C ₆ -C ₁₁	σ^*	0.02509	1.92	1.32	0.045
-	-		C ₁₃ -N ₁₄	σ^*	0.05686	1.78	1.26	0.043
-	-		C ₁₃ -C ₁₆	σ^*	0.01378	2.75	1.27	0.053
-	-		N ₁₅ -C ₂₄	σ^*	0.02851	3.17	1.15	0.054
C ₁₁ -N ₁₄	π	1.85722	C ₁ -C ₆	π^*	0.42501	6.46	0.37	0.047
-	-		C ₁₁ -N ₁₄	π^*	0.63126	2.16	0.30	0.026
-	-		C ₁₂ -C ₁₃	π^*	0.33874	16.18	0.38	0.074
C ₁₂ -C ₁₃	π	1.82279	C ₁₁ -N ₁₄	π^*	0.63126	14.48	0.23	0.059
C ₁₃ -C ₁₄	σ	1.97914	C ₆ -C ₁₁	σ^*	0.02509	3.91	1.28	0.063
-	-		C ₁₁ -N ₁₄	σ^*	0.05087	1.91	1.26	0.044
-	-		C ₁₁ -N ₁₅	σ^*	0.02988	0.78	1.23	0.028
-	-		C ₁₂ -C ₁₃	σ^*	0.02422	1.20	1.40	0.037
-	-		C ₁₂ -N ₁₅	σ^*	0.03288	0.85	1.23	0.029
-	-		C ₁₂ -C ₂₀	σ^*	0.01559	4.44	1.20	0.065
C ₂₄ -C ₂₇	σ	1.98273	C ₁₁ -N ₁₅	σ^*	0.02988	0.66	1.06	0.024
-	-		C ₁₂ -N ₁₅	σ^*	0.03288	0.70	1.06	0.024
-	-		C ₂₇ -C ₃₀	σ^*	0.01604	0.72	0.99	0.024
-	-		C ₃₀ -C ₃₃	σ^*	0.00635	1.70	1.00	0.037
LPN ₁₅	σ	1.58562	C ₁₁ -N ₁₄	π^*	0.63126	51.14	0.23	0.102
-	-		C ₁₂ -C ₁₃	π^*	0.33874	34.72	0.30	0.093
-	-		C ₂₄ -C ₂₇	σ^*	0.02279	6.53	0.62	0.063
LPO ₃₇	σ	1.98038	C ₁₁ -N ₁₄	σ^*	0.05087	5.23	1.21	0.072
-	-		C ₁₃ -N ₁₄	σ^*	0.05686	3.41	1.18	0.057
LPO ₃₇	π	1.91090	C ₁₁ -N ₁₄	σ^*	0.05087	10.05	0.69	0.075

-	-		C ₁₃ -N ₁₄	σ^*	0.05686	10.82	0.65	0.075
LPO ₃₇	n	1.72131	C ₁₁ -N ₁₄	π^*	0.63126	55.46	0.17	0.095
LPO ₃₈	σ	1.98033	C ₃ -C ₄	σ^*	0.02733	6.24	1.16	0.076
LPO ₃₈	π	1.87071	C ₂ -C ₃	π^*	0.39695	27.89	0.35	0.095

^aE(2) means energy of hyperconjugative interactions (stabilization energy).

^bEnergy difference between donor and acceptor i and j NBO orbitals.

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

Table 6. NBO results showing the formation of Lewis and non-Lewis orbitals.

Bond (A-B)	ED/energy (a.u.)	EDA%	EDB%	NBO	s%	p%
πC_2-C_3	1.97438	53.34	46.66	$0.7303(sp^{1.00})C+$	0.00	100.00
-	-0.69124	-	-	$0.6831(sp^{1.00})C$	0.00	100.00
σC_3-C_4	1.98132	50.16	49.84	$0.7083(sp^{1.63})C+$	37.94	62.06
-	-0.69807	-	-	$0.7059(sp^{1.92})C$	34.25	65.75
$\sigma C_{11}-N_{14}$	1.98202	37.96	62.04	$0.6161(sp^{2.38})C+$	29.52	70.48
-	-0.81721	-	-	$0.7877(sp^{1.78})N$	35.96	64.04
$\pi C_{11}-N_{14}$	1.85722	38.09	61.91	$0.6172(sp^{99.99})C+$	0.08	99.92
-	-0.32988	-	-	$0.7868(sp^{1.00})N$	0.00	100.00
$\pi C_{12}-C_{13}$	1.82279	49.76	50.24	$0.7054(sp^{1.00})C+$	0.01	99.99
-	-0.25982	-	-	$0.7088(sp^{1.00})C$	0.00	100.00
$\sigma C_{13}-N_{14}$	1.97914	37.53	62.47	$0.6126(sp^{2.94})C+$	25.38	74.62
-	-0.77528	-	-	$0.7904(sp^{1.91})N$	34.37	65.63
$\sigma C_{24}-C_{27}$	1.98273	50.57	49.43	$0.7111(sp^{2.43})C+$	29.18	70.82
-	-0.61154	-	-	$0.7031(sp^{2.76})C$	26.57	73.43
$n_1 N_{15}$	1.58562	-	-	$sp^{99.99}$	0.04	99.96
-	-0.25329	-	-	-	-	-
$n_1 O_{37}$	1.98038	-	-	$sp^{0.26}$	79.06	20.94
-	-0.72830	-	-	-	-	-
$n_2 O_{37}$	1.91090	-	-	$sp^{99.99}$	0.04	99.96
-	-0.20280	-	-	-	-	-
$n_3 O_{37}$	1.72131	-	-	$sp^{1.00}$	0.00	100.00
-	-0.19411	-	-	-	-	-
$n_1 O_{38}$	1.98033	-	-	$sp^{1.23}$	44.73	55.27
-	-0.58909	-	-	-	-	-
$n_2 O_{38}$	1.87071	-	-	$sp^{1.00}$	0.00	100.00
-	-0.31149	-	-	-	-	-

Table 7. The charge distribution calculated by the Mulliken and natural bond orbital (NBO) methods.

<u>Atoms</u>	<u>Atomic charges</u> (Mulliken)	<u>Natural charges</u>
C ₁	-0.187709	-0.21081
C ₂	-0.174961	-0.28617
C ₃	0.356813	0.32895
C ₄	-0.204898	-0.31249
C ₅	-0.164827	-0.17757
C ₆	0.113806	-0.13741
H ₇	0.127568	0.22494
H ₈	0.137027	0.24582
H ₉	0.122154	0.23083
H ₁₀	0.188376	0.27540
C ₁₁	0.431995	0.34588
C ₁₂	0.266873	0.13872
C ₁₃	0.262245	0.11149
N ₁₄	-0.121278	0.04721
N ₁₅	-0.533913	-0.37943
C ₁₆	-0.511355	-0.70392
H ₁₇	0.180532	0.25836
H ₁₈	0.179126	0.25751
H ₁₉	0.143314	0.23314
C ₂₀	-0.543722	-0.70667
H ₂₁	0.175509	0.25532
H ₂₂	0.165826	0.24176
H ₂₃	0.172154	0.24413
C ₂₄	-0.172338	-0.25344
H ₂₅	0.177578	0.25609
H ₂₆	0.159532	0.24027
C ₂₇	-0.256858	-0.46652
H ₂₈	0.140371	0.23858
H ₂₉	0.161529	0.23228

C ₃₀	-0.263689	-0.46014
H ₃₁	0.133603	0.22435
H ₃₂	0.153018	0.23394
C ₃₃	-0.445147	-0.67375
H ₃₄	0.149140	0.23612
H ₃₅	0.144807	0.22582
H ₃₆	0.150401	0.22905
O ₃₇	-0.578061	-0.58923
O ₃₈	-0.643201	-0.68445
H ₃₉	0.408660	0.48599

Table 8

The binding affinity values of different poses of the title compound predicted by AutodockVina.

Mode	Affinity (kcal/mol)	Distance from best mode (Å)	
		RMSD l.b.	RMSD u.b.
-	-		
1	-6.3	0.000	0.000
2	-5.9	23.802	26.545
3	-5.8	24.468	27.380
4	-5.6	2.853	5.312
5	-5.5	24.281	26.447
6	-5.2	22.815	24.302
7	-5.2	2.992	5.209
8	-5.0	2.850	4.218
9	-5.0	3.314	4.925

Fig.1 Optimized geometry of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide

167.05 ALIE [kcal/mol] 378.11

Fig.2 ALIE surface of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide molecule

Fig. 3 Intra-molecular non-covalent interactions of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide molecule

Fig.4 Fukui functions of title molecule a) f^- and b) f^+ functions

Bond	BDE [kcal/mol]
1	113.97
2	119.94
3	94.35
4	89.84
5	83.94
6	103.62
7	103.54
8	103.32
9	107.95
10	113.05
11	101.89
12	105.50
13	112.73
14	46.95
15	76.07
16	85.24
17	89.11

Fig.5 BDE of all single acyclic bonds of 1-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl-imidazole 3-oxide molecule

Fig.6 RDFs of a) carbon and b) non-carbon atoms with significant interactions with water

Fig.7 Surface view of receptor with docked ligand embedded in the active site.

Highlights

- * IR, Raman spectra and MEP, NBO analysis were reported.
- * The wavenumbers are calculated theoretically.
- * The geometrical parameters are in agreement with that of similar derivatives.
- * The title compound might exhibit inhibitory activity against CDK inhibitor.