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Reference:

Murthy P. Krishna, Mary Y. Sheena, Suneetha V., Panicker C. Yohannan, Armakovic Stevan, Armakovic Sanja J., Giri L., Suchetan P. A., Van Alsenoy Christian.-
Towards the new heterocycle based molecule : synthesis, characterization and reactivity study
Journal of molecular structure - ISSN 0022-2860 - 1137(2017), p. 589-605
Full text (Publisher's DOI): <https://doi.org/10.1016/J.MOLSTRUC.2017.02.071>
To cite this reference: <http://hdl.handle.net/10067/1436380151162165141>

Accepted Manuscript

Towards the new heterocycle based molecule: Synthesis, characterization and reactivity study

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PII: S0022-2860(17)30230-2

DOI: [10.1016/j.molstruc.2017.02.071](https://doi.org/10.1016/j.molstruc.2017.02.071)

Reference: MOLSTR 23465

To appear in: *Journal of Molecular Structure*

Received Date: 10 December 2016

Revised Date: 18 January 2017

Accepted Date: 19 February 2017

Please cite this article as: P.K. Murthy, Y. Sheena Mary, V. Suneetha, C.Y. Panicker, S. Armaković, S.J. Armaković, L. Giri, P.A. Suchetan, C. Van Alsenoy, Towards the new heterocycle based molecule: Synthesis, characterization and reactivity study, *Journal of Molecular Structure* (2017), doi: 10.1016/j.molstruc.2017.02.071.

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Towards the new heterocycle based molecule: synthesis, characterization and reactivity study

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Abstract

4-Chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (CFDPPO) have been synthesized by hydride transfer from Et₃SiH to carbenium ions(reduction reaction), which is formed by reaction between 4-chloro-2-(3-fluorophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one with TFA, the single crystals were grown in acetonitrile by slow evaporation technique at room temperature and characterized by single crystal X-ray diffraction, FT-IR, FT-Raman, ¹H-NMR, ¹³C-NMR and ESI-MS. The experimental vibrational spectra were compared with the calculated spectra and each vibrational wavenumber was assigned on the basis of potential energy distribution (PED). Gauge-including atomic orbital ¹H-NMR and ¹³C-NMR chemical shifts calculations were carried out and compared with experimental data. The HOMO and LUMO analysis is used to determine

the charge transfer within the molecule. The stability of the molecule arising from hyper-conjugative interactions and charge delocalization has been analysed using NBO analysis. First hyperpolarizability is calculated in order to find its role in non-linear optics. Besides molecular electrostatic potential (MEP), global reactivity descriptors, thermodynamic properties, and Mullikan charge analysis of the title compound were computed with the same method in gas phase, theoretically. Further, employing combination of DFT calculations and molecular dynamics (MD) simulations, we have investigated in detail reactive properties of the title molecule. Investigation of local reactive properties encompassed calculations of average local ionization energies (ALIE) and Fukui functions. Stability in water has been investigated by calculations of radial distribution functions (RDF), while sensitivity towards the mechanism of autoxidation has been investigated by calculations of bond dissociation energies (BDE). The docked ligand forms a stable complex with human $\alpha 9$ nicotinic acetylcholine receptor antagonist and can be a lead compound for developing new anti-cancerous drug.

Keywords: Single crystal XRD; DFT; ALIE; RDF; molecular docking.

1. Introduction

Various studies in medicinal chemistry research have exposed that the existence of halogens in organic molecules often progresses their biological activities. An extensive variety of halogenated compounds with diverse biological activities are known till date, for example anticancer [1], antiviral [2], anti-tuberculosis [3], anti-malarial [4,5], antifungal agents and anti-diabetic agents [6]. Heterocycles represent the most general structural units in several natural and synthetic bioactive compounds [7-9]. Especially, substituted 2,3-dihydro-1H-pyrrolo[3,4-c]pyridines are important representatives of fused heterocyclic systems due to their occurrence in various biologically active substances. In particular, pyrrolo[3,4-c]pyridine derivatives were found to show analgesic, hypnotic, and psychotropic effects [10,11]. The understanding of their structure, molecular properties as well as the nature of reaction mechanism they undergo have great importance and have been the subject of many experimental and theoretical studies. In this study, we first synthesized 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (CFPDPPPO), then the geometrical parameters, fundamental wavenumbers, molecular electrostatic potential and thermodynamic properties in the ground state have been calculated by using the DFT/B3LYP method with 6-311++G(d,p) as basis set. HOMO, LUMO analysis have been used to reveal information regarding charge transfer within the molecule to understand the biological activity of the title compound. The change in electron density (ED) in the anti-bonding orbitals and stabilization

energies $E(2)$ of the molecule have been calculated by natural bond orbital (NBO) analysis to give clear evidence of stabilization. Molecule investigated in the present study could serve as an active component of some new pharmaceutical formulation. Stability and degradation properties of such molecules are of particular interest, from both practical and ecological aspects. From one side pharmaceutically active molecules should be highly stable in order to perform necessary actions. On the other side great stability hardens their degradation once they are accumulated in different types of water where natural conditions are not effective enough to decompose them [12]. Great stability of pharmaceutical molecules also leads to the situation that conventional water purification methods are also not efficient in their case [13, 14]. Advanced oxidation processes turned out to be very efficient when it comes to the forced degradation of organic pharmaceutical pollutants [13, 15-20]. Since these experimental procedures are long and complex, DFT calculations and MD simulations [21-24] are vastly employed in order to anticipate reactivity of target molecules and in such way contribute to the development of forced degradation studies.

2. Experimental and computational methods

2.1 General remarks

All anhydrous reactions were carried out by standard procedures under nitrogen atmosphere to avoid moisture. All other chemicals were procured from commercial sources and used as received. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates. TLC plates were visualized by exposing UV light or by iodine vapours. The ^1H -NMR and ^{13}C -NMR spectra were recorded on Bruker AMX 400 MHz spectrometer in $\text{DMSO}-d_6$. Chemical shifts are given in the δ scale in parts per million (ppm). Proton resonances are designated as singlet(s), doublet(d), triplet(t), multiplet(m) and doublet of doublet(dd). FT-IR spectrum (Fig. S1- supporting material) of the title compound was recorded using KBr pellets in the range $4000\text{-}500\text{ cm}^{-1}$ region with a Bruker Alpha-T module. FT-Raman spectrum (Fig. S2 – supporting material) of the title compound was recorded using 1064 nm line of Nd:YAG laser as excitation wavelength in the region $4000\text{-}0\text{ cm}^{-1}$ on a Thermo-Nicolet 6700 FT-Raman Spectrometer model. Electron impact mass spectra (EI-MS) were obtained on LC Agilent 1100 series Mass Spectrometer.

2.2 Synthesis

To a stirred solution of 4-chloro-2-(3-fluorophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (1.0g , 3.59 mmol) in DCM (20 mL) was cooled to 0°C . To this add triethylsilane (13.21 mL, 82.73 mmol) and trifluoroacetic acid (11.5 mL, excess), at same

temperature. Then, the solution was stirred for 10 h at 45°C. The reaction mixture was cooled to room temperature, evaporated to remove volatiles and diluted with ethyl acetate (20 mL), and poured into saturated aqueous NaHCO₃ solution to adjust pH7 and the organics was extracted with ethyl acetate (2×20 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure to afford CFPDPPO (0.61 g, 64.7%) as off white solid (scheme – supporting information-Fig.S3) [25]. Single crystals suitable for XRD were obtained by slow evaporation of an acetonitrile solution at room temperature. Mass spectrum (Fig.S4-supporting information), m/z : 263.1 [M+H]⁺

2.3 X-ray crystallography

A colourless, needle shaped single crystal of the title compound, with dimensions of 0.300 mm × 0.250 mm × 0.200 mm was selected and mounted on a Bruker APEX-II CCD diffractometer with monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) at 273(2) K. The data were processed with SAINT and corrected for absorption using SADABS [26]. The structure was solved by direct method using the program SHELXL [27] and was refined by full-matrix least squares technique on F² using anisotropic displacement parameters for all non-hydrogen atoms. The ORTEP diagram of the compound is given in Fig. S5 (supporting material) and the packing of molecules in the crystal lattice are in shown in Fig. S6 (supporting material). The crystallographic data and refinement parameters are summarized in table 1.

3. Computational details

The calculations based on DFT method have been used in many areas [28-31]; it has become a progressively beneficial tool for theoretical studies. The success of DFT is mainly due to the point that it expresses about small molecules more reliably than Hartree-Fock theory and also computationally less challenging than wave function based methods with enclosure of electron correlation [32, 33]. The DFT calculations with the hybrid exchange correlation functional B3LYP (Becke's three parameter (B3) exchange in conjunction with the Lee-Yang-Parr's (LYP) correlation functional) which are specifically significant in systems comprising of extensive electron conjugation and/or electron lone pairs [34-37]. To get further insight into the effect of molecular structure and electron distribution on the spectroscopic properties of the title compound, the geometry (Fig. 1) was optimized in ground state. All calculations were performed within the density functional theory (DFT) with exchange correlation hybrid functional: B3LYP (three-parameter exchange functional of Becke B3 [38] combined with the Lee-Yang-Parr correlation functional LYP [39] using the extended basis sets with polarization and diffuse functions 6-311+ +G(d,p). For acuminous

visualization, we employ the package GAUSSVIEW-5 [40]. The calculated wavenumbers are scaled by a scaling factor of 0.9613 to obtain a better agreement with the experimental results [41]. The calculated wavenumbers were assigned by means of the potential energy distribution (PED) using GAR2PED program [42]. Theoretical ^1H -NMR and ^{13}C -NMR chemical shifts were calculated in ground state by using GIAO approach and chemical shifts were calculated with reference to TMS. Time dependent density functional theory (TDDFT) [43] approach has been applied to assign the electronic transitions in UV-Visible spectra. The partial atomic charges are calculated same basic level using Mulliken population analysis and electrostatic potential (ESP). The theoretical reactivity indices defined by Parr and Pearson [44] the electronegativity ($\chi = -(\text{E}_{\text{LUMO}} + \text{E}_{\text{HOMO}})/2$); hardness ($\eta = (\text{E}_{\text{LUMO}} - \text{E}_{\text{HOMO}})/2$); and electrophilicity index ($\omega = \chi^2/2\eta$). Schrödinger Materials Science Suite 2015-4 was also used in this study for the investigation of reactivity of the title molecule. Jaguar 9.0 [45] program was used for DFT calculations, while Desmond [46-49] program was used for MD simulations. In the case of DFT calculations a well-known B3LYP exchange-correlation functional [38] has been employed together with 6-311++G(d,p), 6-31+G(d,p) and 6-311G(d,p) basis sets for the calculations of ALIE, Fukui functions and BDEs, respectively. OPLS 2005 force field [50] was for MD simulations with Desmond program with simulation time set to 10 ns. Temperature was set to 300 K, while pressure was to 1.0325 bar. Cut off radius was set to 12 Å. System was of isothermal-isobaric (NPT) ensemble class. For the solvent a simple point charge (SPC) model [51] was used. MD simulation was done by placing of one CFPDPPO molecule into the cubic box with ~3000 water molecules. Electron density analysis developed by Johnson et al. [52, 53] and implemented in Jaguar program was used for the determination of noncovalent interactions. Maestro GUI [54] was used for the preparation of input files and analysis of results when Schrödinger Materials Science Suite 2015-4 was used.

4. Hirshfeld surface Analysis

We examined molecular surfaces, the nature of packing of molecules in their crystal lattice structure, highlighting the contribution of significant inter molecular interactions between molecules that are responsible for the molecular arrangement in the crystalline state. Hirshfeld surfaces [55-57] and the related 2D fingerprint plots [58-60] are unique for any crystal structure, provide a quantitative measure of the intermolecular interactions on the surface [61, 62], calculated by using Crystal Explorer [63] and which accepts a structure input file in the CIF format. Two dimensional (2D) fingerprints maps were obtained by calculating two distances, d_e , the distance from the point to the nearest nucleus exterior to the

surface, and d_i , the distance to the nearest nucleus interior to the surface, are defined. They are mapped using a fixed color scale red, white, blue, where red highlights are contacts shorter than van der Waals (vdW) radii sum which is represented by negative sign values of d_{norm} , white for contacts around vdW separation with d_{norm} values equal to zero, and blue for contacts longer than vdW sum with positive sign d_{norm} values.

5. Results and discussion

In the following discussion, the rings C6-C7-C8-N4-C14-C15, C6-C7-C5-N3-C11 and C9-C10-C16-C17-C18-C12 are designated as PhI, PhII and PhIII, respectively.

5.1 Crystal structural analysis

The compound crystallizes in monoclinic space group $P21/c$ with $a = 7.388(1)$, $b = 12.949(1)$, $c = 11.938(1)$, $\beta = 99.33(2)$ and $Z = 4$. The molecule of the title compound is almost planar, the RMSD of all the non-hydrogen atoms is $0.040 \text{ \AA}$ and the angle between the planes defined by the fluorobenzene and 2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine rings (considering the non hydrogen ring atoms) is $4.12(12)^\circ$. An intra-molecular $\text{C}_{15}\text{-H}_{225}\dots\text{O}_2$ hydrogen bond with a graph set notation $S(6)$ is observed which stabilize the molecular conformation [64]. In the crystal, molecules are connected into dimers via a pair of $\pi(\text{benzene})\dots\pi(\text{pyridine})$ interactions, and these dimers form ladder like architecture via short $\text{Cl}\dots\text{Cl}$ interactions.

5.2 Geometrical parameters

The molecular structure of the title compound optimise in ground state by using DFT/B3LYP/6-311++G(d,p) level of theory. The optimized parameters of the title compound (bond length, bond angles) along with their experimental counterparts are listed in Table 2. The optimized title compound possesses C1 symmetry, dipole moment of 0.6087 Debye and ground state energy of -1245.2177 a.u. The C-C bond lengths (DFT/XRD) in the phenyl ring of the title compound are in range 1.3831-1.4059/1.3634-1.3963 $\text{\AA}$ and for benzene the C-C bond length is 1.399 $\text{\AA}$ [65]. The bond lengths (DFT/XRD) of pyridine ring are C₇-C₈, C₈-N₄, C₁₄-C₁₅, C₁₄-N₄, C₁₅-C₆, C₆-C₇, 1.3901/1.3783, 1.3160/1.3223, 1.3924/1.3783, 1.3434/1.3383, 1.3892/1.3823, 1.3843/1.3763 $\text{\AA}$ are close to the reported values. The C-Cl bond length (DFT/XRD) in pyridine ring is 1.7601/1.7322 $\text{\AA}$ which are good agreement with reported value [66]. For the title compound, the C-N bond length (DFT/XRD) C₉-N₃ is 1.4138/1.4183 $\text{\AA}$ shorter than the normal C-N bond length of 1.4900 $\text{\AA}$ [67]. The C=O bond length (DFT/XRD) C₁₁-O₂ = 1.2135/1.2143 $\text{\AA}$ which is in agreement with the reported values [68]. The dihedral angle between the fluorobenzene and 2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine

rings (DFT/XRD), $C_{10}-C_9-N_3-C_{11}$, $C_{12}-C_9-N_3-C_5$ were $175.9/179.5^\circ$ and $176.7/179.3^\circ$ respectively, it shows two rings are in planar.

At C_8 and C_{16} , the bond angles (DFT/XRD), $N_4-C_8-C_7$ and $C_{10}-C_{16}-C_{17}$ are respectively, $123.0/124.0^\circ$ and $123.1/123.3^\circ$ and this enhancement of angle from 120° is due to the presence electronegative chlorine Cl1 and F13 atoms. The interaction between the rings PhII and PhIII is evident from the bond angles (DFT/XRD), $C_{10}-C_9-C_{12} = 119.1/119.3^\circ$, $C_{10}-C_9-N_3 = 118.9/118.4^\circ$, $C_{12}-C_9-N_3 = 122.0/122.3^\circ$, $C_5-N_3-C_{11} = 112.3/112.5^\circ$, $C_5-N_3-C_9 = 121.2/120.7^\circ$ and $C_{11}-N_3-C_9 = 126.6/126.7^\circ$. The interaction between O_2 and $H_{23,25}$ atoms are evident from the bond angles (DFT/XRD), $C_6-C_{11}-N_3 = 105.7/106.0^\circ$, $C_6-C_{11}-O_2 = 126.6/126.3^\circ$ and $N_3-C_{11}-O_2 = 127.8/127.6^\circ$.

The Hirshfeld surfaces of the title compound is illustrated in Fig. 2, showing surfaces that have been mapped over a d_{norm} range of -0.05 - 1.130 Å, shape index -1.0 - 1.0 Å and curvedness -4.0 - 0.4 Å. Red spots near chlorine atoms connected with the chlorine bonds are also clearly seen $C8-C11 \cdots Cl1^i$ 3.379 Å (Fig. 2). The relative contribution of the different interactions to the Hirshfeld surface was calculated for title compound. It is evident from Fig. 2 that the $H \cdots H$ contacts can account for about 22.4% of the Hirshfeld surface area. The remaining contribution was mostly due to $H-C$ 12.5%, $H-Cl$ 11.6%, $H-F$ 10.3%, $H-O$ 9.9%, $H-N$ 9.0%, interactions, with only minor contribution from $C-Cl$, $C-N$, $C-O$ and $Cl-Cl$ (maximum 7.3%).

5.3 IR and Raman spectra

The calculated (scaled) wavenumbers, observed IR, Raman bands and assignments are presented in Table 3. In the present case the band at 1235 cm^{-1} in the IR spectrum and 1232 cm^{-1} (DFT) with IR intensity, 41.25, Raman activity, 80.78 and a PED of 46% is assigned at the C-F stretching mode which is expected in the in the region 1270 - 1100 cm^{-1} [68]. The reported values of CF stretching modes are at 1214 cm^{-1} (IR), 1216 cm^{-1} (Raman) and 1218 cm^{-1} (DFT) [69] and at 1225 cm^{-1} in the IR spectrum and 1223 cm^{-1} (DFT) [70]. The C-Cl stretching mode is assigned at 670 cm^{-1} in the Raman spectrum and at 666 cm^{-1} theoretically with IR intensity 18.51, Raman activity 0.15 and a PED of 42% for the title compound which is expected in the region 710 - 505 cm^{-1} [71] and in agreement with reported values [72]. For the title compound, the C=O stretching and deformation modes are assigned at 1708 cm^{-1} (IR), 1698 cm^{-1} (Raman), 1701 cm^{-1} (DFT) and 774 , 706 cm^{-1} (IR), 744 , 706 cm^{-1} (Raman), 742 , 706 cm^{-1} (DFT) which are in agreement with reported values, 1699 , 760 , 664 cm^{-1} (DFT) [73]. The C=O stretching mode has an IR intensity of 350.34 and Raman activity of 122.23 and a PED 77%. The C=O deformations modes has IR intensities and Raman

activities less than 10 and the PEDs are 30 and 39%. For the title compound, the C-N stretching modes are observed at 1277 cm^{-1} in the IR spectrum, $1275, 1119\text{ cm}^{-1}$ in the Raman spectrum and at $1336, 1279, 1119\text{ cm}^{-1}$ theoretically with PEDs, 33, 42 and 56% [71]. The IR intensities and Raman activities of the C-N stretching modes are, 222.30, 35.13, 17.30 and 532.81, 126.55, 15.33, respectively. For the title compound, the CH_2 modes observed at $2955, 2915\text{ cm}^{-1}$ (IR), $2935, 2909\text{ cm}^{-1}$ (Raman), $2942, 2911\text{ cm}^{-1}$ (DFT) (stretching modes) and $1444, 1162, 980\text{ cm}^{-1}$ (IR), $1450, 980\text{ cm}^{-1}$ (Raman), $1441, 1336, 1164, 978\text{ cm}^{-1}$ (DFT) (deformation modes) as expected in literature [71].

For the title compound, the phenyl C-H stretching modes are assigned at $3122, 3086\text{ cm}^{-1}$ (IR), $3122, 3087, 3065\text{ cm}^{-1}$ (Raman) and $3132, 3101, 3088, 3061\text{ cm}^{-1}$ (DFT) as expected [71]. The PEDs of these modes are almost 100%. The phenyl ring stretching modes are expected in the range $1615\text{-}1260\text{ cm}^{-1}$ [71] and for the title compound, the bands observed $1586, 1461, 1301\text{ cm}^{-1}$ (IR), $1600, 1562, 1302\text{ cm}^{-1}$ (Raman) and in the range $1587\text{-}1294\text{ cm}^{-1}$ theoretically as assigned as these modes. The sixth phenyl ring stretching mode or ring breathing mode appears as a weak band near 1000 cm^{-1} in 1,3-di substituted benzene and in the present case this mode is assigned at 974 cm^{-1} theoretically as expected [71, 74]. For the title compound, the ring breathing mode has low IR intensity (1.45) and a high Raman activity (84.00) according to the calculations and a PED of 41%. The reported value of the ring breathing mode is at 973 cm^{-1} [75]. For the title compound, the in-plane and out-of-plane C-H modes of the phenyl ring are assigned at $1277, 1162, 1060\text{ cm}^{-1}$ (IR), $1265, 1060\text{ cm}^{-1}$ (Raman), $1279, 1164, 1138, 1064\text{ cm}^{-1}$ (DFT) (in-plane deformations) and $877, 764\text{ cm}^{-1}$ (IR), 872 cm^{-1} (Raman), $955, 874, 881, 762\text{ cm}^{-1}$ (DFT) (out-of-plane deformations) as expected [71].

The CH stretching modes of pyridine [76] are usually observed in the range $3000\text{-}3100\text{ cm}^{-1}$. In the present case, the bands observed at $3125, 3074\text{ cm}^{-1}$ in the IR spectrum and at $3109, 3050, 3020\text{ cm}^{-1}$ in the Raman spectrum are assigned to the CH stretching modes of the pyridine ring. The calculated values of these modes are $3081, 3079, 3049, 3029\text{ cm}^{-1}$. Ring stretching vibrations [77] of pyridine occur in the spectral region $1600\text{-}1300\text{ cm}^{-1}$. The bands at $1632, 1602, 1486, 1433\text{ cm}^{-1}$ in the IR spectrum and at $1637, 1610, 1480\text{ cm}^{-1}$ in the Raman spectrum are assigned as the pyridine ring stretching modes which are in agreement with the reported values [78]. The ring breathing mode [79] is observed as a strong band at 991 cm^{-1} in the Raman spectrum and the calculated value is 990 cm^{-1} and at 1022 cm^{-1} in the IR spectrum, 1020 cm^{-1} in the Raman spectrum.

5.4 NMR spectra

Precise prediction of molecular geometry measurement is necessary for reliable computations of magnetic properties, hence after performing the full geometry optimization of title compound using DFT at B3LYP/6-311++G(d,p) method. The experimental NMR spectra are given in Figs. S7 and S8 (supporting information). The results in table 4 show that the range ^{13}C -NMR chemical shift of typical organic molecule is usually >100 ppm [80-82]. The Cl and F group which is an electronegative functional group polarizes the electron distribution, therefore the calculated ^{13}C -NMR chemical shift value of C_8 and C_{16} bonded to Cl and F group is too high, observed de-shielded region at δ 149.98 and 161.02, while which was calculated at δ 160.08 and 172.31, respectively. Due to the withdrawing nature in the adjacent position, the chemical shift is in the de-shielded region. The signal at 164.40/169.28 (experimental/theoretical) is assigned to the carbonyl carbon C_{11} . Carbon atom (C_5) of the methylene group resonates at 49.47 ppm and show good agreement with computed value at 51.56 ppm. In the ^1H -NMR chemical shift values show three ranges; the first one is around 7.05-7.89/6.99-9.33 (experimental/theoretical) ppm due to proton on benzene ring, the second one is around 7.79-8.61/7.33-8.63 (experimental/theoretical) ppm due to proton on pyridine ring and the last one is 5.09/4.63 (experimental/theoretical) ppm due to the protons of methylene group.

5.5 UV-Visible spectral analysis

In the present study, the maximum absorption wavelengths, excitation energies and oscillator strengths of the title molecules in the gaseous phase are computed using TD-DFT/B3LYP/6-311++G(d,p) method (table 5). The simulated UV-Visible spectrum in the gaseous phase is shown in Fig.S9. Electronic transitions are usually classified according to the orbital engaged or to specific parts of the molecule involved. Common types of electronic transitions in organic compounds are π - π^* , n - π^* , and $\pi^*(\text{acceptor})$ - $\pi(\text{donor})$. Most of the electronic transitions are mainly contributed by the LUMOs-HOMOs transition. The UV-visible bands of title compound are observed at 325 nm, 285 nm and 272 nm with oscillator strength 0.2091, 0.0276, 0.0668 with 3.8040 eV, 4.3460 eV and 4.5534 eV, respectively. In view of calculated absorption spectra, the maximum absorption wavelength corresponds to the electronic transition from the HOMO to LUMO with maximum contribution.

5.6 Frontier molecular orbital analysis

Highest occupied molecular orbital (HOMO) energy describes the ability of electron donating, lowest unoccupied molecular orbital (LUMO) energy describes the ability of electron accepting, these orbitals also called as Frontier molecular orbitals (FMOs) and the gap between HOMO-LUMO of the title compound has been calculated by using

DFT/B3LYP/6-311G++(d,p). The energy gap between HOMO-LUMO is very important in term of explaining the spectroscopic properties and chemical behaviour of the compound [83]. The molecular orbital and their properties such as energy are useful for predicting most reactive position in π -electron and conjugated systems [84]. High chemical reactivity and low kinetic stability are associated with a molecule having a small frontier HOMO-LUMO energy gap [85, 86]. The plots of the frontier molecular orbitals HOMO-LUMO is given in Fig. S10 (supporting information). According the results, the title molecule contains 67 occupied molecular orbitals. The negative phase is green and positive one is red. The HOMO is mainly spread on fluorophenyl ring, CH_2 , amide of pyrrolo ring and partially extended to pyridine ring of 4-chloro-1H-pyrrolo[3,4-c]pyridin-3(2H)-one. The LUMO is mainly localized on 4-chloro-1H-pyrrolo[3,4-c]pyridin-3(2H)-one ring and partially extended to phenyl ring. For the title compound, the energies of HOMO and LUMO orbital are -6.7652 eV and -2.4917 eV, frontier orbital energy gap values is -4.2735 respectively for title compound. Lower energy gap between HOMO and LUMO explains the ultimate charge transfer happen within molecule, which influences its biological activities and chemical reactivity [83]. The narrow energy gap between HOMO-LUMO revealed the compound highly reactive, kinetically less stable and also initiates intra molecular charge transfer, which makes the material to be NLO active. The global chemical descriptors associated with a molecule are: ionization potential $I = -E_{\text{HOMO}} = 6.7652$ eV, electron affinity $A = -E_{\text{LUMO}} = 2.4917$ eV, electronegativity $\chi = (I+A)/2 = 4.6284$, global hardness $\eta = (I-A)/2 = 2.1367$, chemical potential $\mu = -(I+A)/2 = -4.6284$ and electrophilicity index $\omega = \mu^2/2\eta = 5.0128$ [87].

Nonlinear optical properties

The dipole moment μ , the mean polarizability α_0 are calculated using Gaussian 09 software and are found to be 0.6087 Debye and 2.7392×10^{-23} e.s.u respectively. The potential application of the title compound in the field of nonlinear optics demands the investigation of its structural and bonding features contributing to the hyperpolarizability enhancement, by analyzing the vibrational modes using the IR and Raman spectrum [88]. The ring stretching bands at 1586, 1301, 1147 cm^{-1} observed in IR spectrum have their counterparts in the Raman spectrum at 1600, 1302, 1150 cm^{-1} , respectively and their intensities in IR and Raman spectra are comparable. The C-N bond lengths in the present case ($\text{C}_5\text{-N}_3 = 1.4704$, $\text{C}_9\text{-N}_3 = 1.4138$, $\text{C}_{11}\text{-N}_3 = 1.3989$, $\text{C}_8\text{-N}_4 = 1.3160$, $\text{C}_{14}\text{-N}_4 = 1.3434$ Å) are intermediate between those of a C-N single bond (1.48 Å) and a C=N double bond (1.28 Å) and therefore, the calculated data suggest an extended π -electron delocalization of the molecular system which is responsible for the nonlinearity of the title compound [89]. The first order hyperpolarizability

of the title compound is calculated and is found to be 11.73×10^{-30} esu and comparable with that of similar derivatives [90,91] and 90.23 times that of the standard NLO material urea (0.13×10^{-30} esu) [92]. The average second hyperpolarizability is $\langle \gamma \rangle = (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz})/5$ [93]. The theoretical second order hyperpolarizability was calculated using the Gaussian09 software and is equal to -13.089×10^{-37} e.s.u.

5.7 Molecular Electrostatic Potential

Molecular electrostatic potential (MEP) mapping in quantum mechanical chemistry is a valuable tool used mainly for calculating sites and relative reactivity towards electrophilic and nucleophilic [94] attack, in studies of biological identification and hydrogen bonding interactions [95, 96]. The negative electrostatic potential and positive electrostatic potential are related through the attraction of proton by intense electron density in the molecule (coloured in shades of red on the EPS surface) and repulsion of the proton by the atomic nuclei in regions of low electron density (coloured in shades of blue on the EPS surface), respectively. Potential increases in the order red < orange < yellow < green < blue, where blue specifies the strongest attraction; red indicates strongest repulsion; and green indicates neutral electrostatic potential region [97]. The MEP of the studied compound calculated using B3LYP method with 6-311++G(d,p) basis set is plotted as 3D and 2D contour map plots in Figs. S11a and S11b (supporting material). From the MEP plot it is clear that the carbonyl groups and N4 of the pyridine ring are the most negative regions, electrophilic regions and the positive region, nucleophilic regions is over the remaining portions of the molecule. The electrophilic and nucleophilic sites give information about the region from where the compound can have non-covalent interactions.

5.8 ALIE surface, Fukui functions and noncovalent interactions

We will further refer to the average local ionization energy (ALIE) quantity, which is useful quantum molecular descriptor for the determination of the molecule sites sensitive towards the electrophilic attacks. ALIE quantity indicates the required amount of energy required for the removal of electron. Thus, molecule sites where ALIE values are the lowest are areas where electrons are the least tightly bound, being the most sensitive towards electrophilic attacks. ALIE was defined by Sjöberg et al. [98, 99] as a sum of orbital energies weighted by the orbital densities according to the following equation:

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

where $\rho_i(\vec{r})$ denotes electronic density of the i -th molecular orbital at the point $\vec{r}$, ε_i denotes orbital energy, while $\rho(\vec{r})$ denotes total electronic density function [100, 101]. ALIE values can be presented for each atom separately or they can be mapped to the electron density surface, which is the method used in this work, Fig. 3. According to the results presented in Fig. 3, beside benzene ring, near vicinity of nitrogen atom N4 is characterized by the lowest ALIE values and therefore could be the molecule site sensitive towards the electrophilic attacks. This molecule site is characterized by the ALIE value of ~ 206 kcal/mol. On the other side the molecule site with the highest ALIE value, ~ 368 kcal/mol, is the fluorine atom. In Fig. 3, one intramolecular noncovalent interaction is also visualized. It is formed between oxygen atom O2 and hydrogen atom H23, with corresponding strength of -0.019 electron/bohr³. Determination of other possibly important reactive centres has been done thanks to the Fukui functions. Fukui functions are defined as the functional derivative of the chemical potential with respect to the external potential [102]. Another interpretation of Fukui functions can be taken into account. Namely, by using the Maxwell relation Fukui function can be presented in the form of derivative of the electronic density with respect to the number of electrons [102, 103]. Fukui functions indicate the changes in electron density resulting from the change in charge. A convenient way to visualize the Fukui functions is also by mapping of their values to the electron density surface. By finite difference approach Fukui functions are calculated in Jaguar program 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 stands for the number of electrons in reference state of the molecule, while δ stands for the fraction of electron which default value is set to be 0.01 [104]. Fukui functions of CFPDPPO molecule are presented in Fig.4. Positive (purple) colour in Fig.4a shows areas where electron density increased after addition of charge, while negative (red) colour in Fig.4b shows areas where electron density decreases after removal of charge. Purple colour in Fig.4a shows that electron density increases, after the increase of charge, in the near vicinity of atoms C11, C15 and, again, N4, determining these atoms as electrophilic ones. On the other side in Fig.4b it can be seen that electron density decreases in the near vicinities of atoms C6, C27 and chlorine Cl1, determining these atoms as nucleophilic ones.

5.9 Mulliken atomic charges

The atomic charge values were obtained by the Mulliken population analysis [105]. Mulliken atomic charge calculation has an important role for the application of quantum chemical calculation of the molecular system. Atomic charge affects dipole moment, polarizability, electronic structure and other molecular properties of the system. Mulliken population analysis of title compound was computed using DFT/B3LYP with 6-311++G(d,p) basis set and are listed in Table 6. C₇ (1.920), C₆ (0.442), C₁₀ (0.343), C₁₇ (0.280) accommodate positive charge and become more acidic. Other C atoms are negative. Moreover, Mulliken atomic charges also show that all the hydrogen atoms have a net positive charge but an H₂₃ atom accommodate more positive atomic charges 0.250, than the other hydrogen atoms and is acidic. The calculated Mulliken charges of O₂, H₂₃ and C₁₂ atoms are determined as -0.282, 0.250 and -0.044 e and these values confirm intramolecular hydrogen bond C₁₂H₂₃...O₂ in solid forms.

5.10 Natural bonding orbital analysis

The natural bond orbital (NBO) calculations were performed using NBO 3.1 program [106] as implemented in the Gaussian03 package at the B3LYP method with the 6-311++G(d,p) (5D, 7F) level for investigating the various interactions [107, 108]. The second-order perturbation theory analysis of Fock-matrix in NBO basis shows strong intermolecular hyper conjugative interactions are formed by orbital overlap between n₁(N₃) and $\pi^*(\text{O-Cl})$, $\pi^*(\text{C-C})$, n₂(O₂), and $\sigma^*(\text{N-Cl})$, $\sigma^*(\text{C-Cl})$, bond orbitals which result in ICT causing stabilization of the system. These interactions are observed as an increase in electron density (ED) in O-Cl, C-C, N-Cl and C-Cl, antibonding orbital that weakens the respective bonds. The strong inter molecular hyper conjugative interactions are: O₂-Cl₁ from N₃ of n₁(N₃)→ $\pi^*(\text{O}_2\text{-Cl}_1)$, C₉-C₁₀ from n₁(N₃) of n₁(N₃)→ $\pi^*(\text{C}_9\text{-C}_{10})$, N₃-Cl₁ from O₂ of n₂(O₂)→ $\sigma^*(\text{N}_3\text{-Cl}_1)$, C₆-Cl₁ from O₂ of n₂(O₂)→ $\sigma^*(\text{C}_6\text{-Cl}_1)$ and C₇-C₈ from N₄ of n₁(N₄)→ $\sigma^*(\text{C}_7\text{-C}_8)$. The electron densities and stabilization energies of these interactions are respectively, 0.30641, 0.42039, 0.09009, 0.07174, 0.04304e and 54.92, 35.32, 28.51, 19.12, 10.07 kJ/mol. These interactions are observed as an increase in electron density (ED) in N-Cl, C-Cl, O-Cl, C-C anti bonding orbitals that weakens the respective bonds. The natural hybrid orbitals with considerable p-characters are n₁(N₃), n₂(O₂) and n₁(N₄). Thus, a very close to pure (almost 100%) p-type lone pair orbital participates in the electron donation to the $\pi^*(\text{O}_2\text{-Cl}_1)$ orbital for n₁(N₃)→ $\pi^*(\text{O}_2\text{-Cl}_1)$, $\pi^*(\text{C}_9\text{-C}_{10})$ orbital for n₁(N₃)→ $\pi^*(\text{C}_9\text{-C}_{10})$, $\sigma^*(\text{N}_3\text{-Cl}_1)$ orbital for n₂(O₂)→ $\sigma^*(\text{N}_3\text{-Cl}_1)$, $\sigma^*(\text{C}_6\text{-Cl}_1)$ orbital for n₂(O₂)→ $\sigma^*(\text{C}_6\text{-Cl}_1)$ interaction in the compound. The results are tabulated in Tables 7 and 8.

5.11 Thermodynamic properties

Thermodynamic data of title compound are very important for to obtain reliable relations among structural, energetic, and reactivity characteristics of the molecules and the Density Functional Theory is a very well-established and efficient tool to predict various statistical thermodynamic properties of molecules. The thermodynamic parameters values of title compound were calculated by B3LYP/6-311++G (d,p) at 298.15 K and 1 atm pressure and listed in Table 9, such as dipole moment, thermal energy and zero point vibrational energy. Scale factors have been recommended [109] for a removal of anharmonicity effect and perfect predictions in determining the zero-point vibrational energies, entropy (S), heat capacity (C) and the enthalpy changes (ΔH) in the temperature range 100–1000 K and listed in Table 9, it can be observed that these thermodynamic parameters increase with rise of temperature due to the fact that the molecular vibrational intensities increase with temperature [110].

5.12 Reactive and degradation properties based on autoxidation and hydrolysis

Taking into account the importance of oxidation reactions in degradation pathways of pharmaceutical molecules and organic materials [111-113], in this work we were also focused to the prediction of sensitivity of CFPDPPO molecule towards the autoxidation mechanism. This information is very important for newly synthesized molecules, as it allows rationalization of procedures related to the forced degradation [114-117]. In general, drug molecules are sensitive towards autoxidation mechanism at certain molecule sites. At these molecule sites BDE for hydrogen abstraction is in the range of 70 to 85 kcal/mol, according to the works of Wright et al. [118] and Gryn'ova et al. [119]. In the same time one should also pay attention to the BDE values between 85 and 90 kcal/mol. BDE values lower than 70 kcal/mol don't indicate sensitivity of drug molecules towards the autoxidation mechanism [31, 118, 120].

In this work results concerning BDE values for hydrogen abstraction and BDE for the rest of the single acyclic bonds of CFPDPPO molecule are presented in Fig.5. Results provided in Fig.5 indicate very interesting situation when it comes to the autoxidation of CFPDPPO molecule. Namely, BDE values of bonds denoted with number one in Fig.5 indicate that CFPDPPO molecule is sensitive towards autoxidation mechanism. Namely, BDE for abstraction of hydrogen atoms H20 and H22 is somewhat lower than 85 kcal/mol indicating good degradation properties. Concerning the rest of the single acyclic bonds the lowest BDE value has been calculated in the case of bond denoted with number eight, meaning that detaching of chlorine atom could follow during the degradation process. In the case of pharmaceutical molecules autoxidation and hydrolysis mechanisms are very

important from the environmental aspect. It is also important to note that these two mechanisms could compete at one molecule site, therefore inhibiting degradation of target molecule. To investigate the sensitivity of CFPDPPO molecule towards the hydrolysis mechanism we have calculated RDFs after MD simulations. RDF, $g(r)$, determines the probability of finding a particle in the distance r from another particle [121]. In this work RDFs have been calculated in function of distance between CFPDPPO's atoms and oxygen atoms of water molecules. The results are presented in Fig.6. Inspection of results presented in Fig.6 indicates that there are ten atoms of CFPDPPO molecule with RDF profiles worth of mentioning. However, in all cases profiles and positions of $g(r)$ curves do not indicate significant interactions with water molecules. Namely, of all carbon atoms (Fig.6a) the most important is the carbon atom C14 characterized with maximal $g(r)$ value of almost 1.3 and located at distance of more than 3.5 Å. RDF of carbon C5, to which are connected hydrogen atoms H20 and H22, indicate very weak interactions with water molecules. As already pointed out two the most important hydrogen atoms from the aspect of autoxidation are atoms H20 and H22. According to the results presented in Fig.6b it can be seen that one of them has RDF in the form of peak. However, $g(r)$ profile of H22 is not sharp and also its maximal $g(r)$ value is located at high distance of more than 2.5 Å. Since strong interactions between hydrogen atoms and water molecules are characterized by peak distances of around 1.6 Å, it can be concluded that H22 has insignificant interactions with water molecules and therefore the autoxidation mechanism remains dominant.

5.13 Molecular docking

Based on the structure of a compound, PASS (Prediction of Activity Spectra) [122] is an online tool which predicts different types of activities. PASS analysis of the title compound predicts activities given in the Table 10, human alpha9 nicotinic acetylcholine receptor antagonist activity with probability to be active (P_a) value of 0.802. The bioactive pyridine moiety is found to enhance the anticancer property of molecules [123] and aminopyridine has attained wide applicability in the synthesis of various pharmaceutical products like anticonvulsants, lipid absorption inhibitors, sodium channel modulators, antibacterial and anticancer agents [124-127]. 2-Amino pyridine derivatives are used in the production of the drugs Piroxicam and Tenoxicam (non-steroidal anti-inflammatory and analgesic drugs), Sulfapyridine (antibacterial drug), and Tripeleminamine (antipruritic and first-generation antihistamine). Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone), has entered several phase I and II clinical trials as an antitumor chemotherapeutic agent [128]. Human non-small cell lung cancer tissues expressed Alpha7-

nicotinic acetylcholine receptor and this expression was higher in smoking patients with squamous carcinomas than those with adenocarcinomas and in male smoking patients than in female. Alpha7-nicotinic acetylcholine receptor antagonists, via mitochondria associated apoptosis, inhibited proliferation of human non-small cell lung cancer primary and established cells [129]. But in breast cancer therapy alpha9 nicotinic acetylcholine receptor is used as target [130]. Thus we choose human alpha9 nicotinic acetylcholine receptor antagonist and is used as target for docking study. High resolution crystal structure of human alpha9 nicotinic acetylcholine receptor antagonist was downloaded from the RSCB protein data bank website with PDB ID: 4UXU. All molecular docking calculations were performed on Auto Dock-Vina software [131] and as reported in literature [70]. The active site of the enzyme was defined to include residues of the active site within the grid size of 40Å×40Å×40Å. The docking protocol was tested by extracting co-crystallized inhibitor from the protein and then docking the same. The docking protocol predicted the same conformation as was present in the crystal structure with RMSD value well within the reliable range of 2Å [132]. Amongst the docked conformations, one which binds well at the active site was analysed for detailed interactions in Discovery Studio Visualizer 4.0 software. Amino acid Lys97, Ala98, Asp99, Ser102 show hydrogen bond interaction and Val93, Lys97, Lys127 forms π -alkyl interactions with docked ligand. The ligand binds at the active site of the substrate by weak non-covalent interactions and these interactions are depicted in Fig.7. The docked ligand forms a stable complex with human alpha9 nicotinic acetylcholine receptor antagonist (Fig.S12 – supporting information) and got a binding affinity value of -7.0 kcal/mol (Table 11). Thus the title compound can be a lead compound for developing new anti-cancerous drug.

Conclusion

The vibrational spectral analysis and single crystal XRD structure of the title compound were carried out for exploring the chemical and pharmacological properties. An intra-molecular C₁₅-H₂₅...O₂ hydrogen bond with a graph set notation S(6) is observed which stabilize the molecular conformation. The theoretically predicted geometrical parameters are in agreement with the XRD data. The first order hyperpolarizability of the title compound is comparable with that of similar derivatives and 90.23 times that of the standard NLO material urea. The HOMO-LUMO energy gap reveals that the compound highly reactive, kinetically less stable and also initiates intra molecular charge transfer, which makes the material to be NLO active. The most electrophilic regions are the carbonyl groups and N₄ of the pyridine ring of the title

compound and nucleophilic regions are over the remaining portions of the molecule. ALIE quantum molecular descriptor indicates that, besides benzene ring, near vicinity of nitrogen atom N4 is sensitive towards electrophilic attacks. Fukui functions determine near vicinities of atoms C₆, C₁₁, C₁₅, C₂₇ and chlorine Cl₁ as possibly important reactive centers. Results also indicate that CFPDPPO molecule is sensitive towards autoxidation mechanism, with the lowest BDE for hydrogen abstraction being lower than 85 kcal/mol. In the same time RDFs after MD simulation indicate that CFPDPPO molecule doesn't have pronounced interactions with water molecules, leaving autoxidation mechanism to be dominant when it comes to the degradation properties. In terms of degradation properties global stability descriptors indicate high stability of the title molecule, thanks to which it can be concluded that forced degradation procedures would probably be necessary for its removal from water. However, the most vulnerable place towards interactions with other chemical species, according to the MEP and ALIE surfaces, is nitrogen atom N4. Therefore, the reactivity of N4 could be of great importance for the ring opening and thus for the degradation of CFPDPPO molecule. Docking studies reveal that the docked ligand forms a stable complex with human alpha9 nicotinic acetylcholine receptor antagonist and can be used as anti-cancerous drug, which requires further experimental study.

Acknowledgments

The authors are highly thankful to Professor V. R. Pedireddi, Solid State & Supramolecular Structural Chemistry Laboratory, School of Basic Sciences, IIT Bhubaneswar for the collection of diffraction data. Part of this work has been performed thanks to the support received from Schrödinger Inc. Part of this study was conducted within the projects supported by the Ministry of Education, Science and Technological Development of Serbia, grant numbers OI 171039 and TR 34019.

Supplementary Material

The cif file of the title compound have been assigned CCDC number 1478447 and can be obtained free of cost on application to CCDC 12 Union Road, Cambridge CB21 3EZ, UK. (Fax: (+44) 1223 336-033; e-mail: data_request@ccdc.cam.ac.uk).

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Figure captions

Fig.1 Optimized geometry of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

Fig.2 Hirshfeld surfaces

Fig.3 ALIE surface of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-

one molecule

Fig.4 Fukui functions a) f^+ and b) f^- of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one molecule

Fig.5 BDEs of all single acyclic bonds of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one molecule

Fig.6 RDFs of atoms of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one molecule with significant interactions with water molecules

Fig.7 The ligand interaction with the amino acids of human $\alpha 9$ nicotinic acetylcholine receptor antagonist

Table 1 Crystal data and structure refinement

Empirical formula	:	C ₁₃ H ₈ ClFN ₂ O
Formula weight	:	262.66
Crystal system	:	Monoclinic
Space group	:	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> /Å	:	7.3880(10)
<i>b</i> /Å	:	12.9490(10)
<i>c</i> /Å	:	11.9380(10)
β /°	:	99.33(2)
Volume/Å ³	:	1127.0(2)
<i>Z</i>	:	4
ρ_{calc} /cm ³	:	1.548
μ /mm ⁻¹	:	0.339
<i>F</i> (000)	:	536.0
2 θ range for data collection/°	:	4.68 to 53.06
Reflections collected	:	20007
Independent reflections	:	2320 [<i>R</i> _{int} = 0.0449, <i>R</i> _{sigma} = N/A]
Data/restraints/parameters	:	2320/0/163
Goodness-of-fit on <i>F</i> ²	:	0.907
Final <i>R</i> indexes [<i>I</i> ≥ 2σ (<i>I</i>)]	:	<i>R</i> ₁ = 0.0535, <i>wR</i> ₂ = 0.1519
Final <i>R</i> indexes [all data]	:	<i>R</i> ₁ = 0.0635, <i>wR</i> ₂ = 0.1628
<u>Largest diff. peak/hole / e Å⁻³</u>	:	<u>0.67/-0.63</u>

Table 10

PASS prediction for the activity spectrum of the title compound. Pa represents probability to be active and Pi represents probability to be inactive.

<u>Pa</u>	<u>Pi</u>	<u>Activity</u>
0.802	0.010	Nicotinic alpha2beta2 receptor antagonist
0.735	0.002	CF transmembrane conductance regulator agonist
0.679	0.003	Antiemetic
0.665	0.005	5 Hydroxytryptamine agonist
0.635	0.056	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0.566	0.017	Analgesic. non-opioid
0.537	0.006	GABA receptor agonist
0.518	0.034	Analgesic
0.472	0.005	GABA A receptor agonist
0.448	0.015	Antiepileptic
0.437	0.011	Antineoplastic alkaloid
0.456	0.031	Anxiolytic
0.436	0.013	Glycogen synthase stimulant
0.436	0.025	Antineoplastic (solid tumors)
0.405	0.004	K(Ca) 3.1 channel activator
0.405	0.004	Potassium channel intermediate-conductance Ca-activated activator
0.423	0.035	Arylmalonate decarboxylase inhibitor
0.451	0.076	HIF1A expression inhibitor
<u>0.366</u>	<u>0.002</u>	<u>Nicotinic alpha3beta4 receptor agonist</u>

Table 12

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

Mode	Affinity (kcal/mol)	Distance from best mode (Å)	
		RMSD l.b.	RMSD u.b.
-	-		
1	-7.0	0.000	0.000
2	-6.8	3.684	5.237
3	-6.6	15.968	17.074
4	-6.6	3.812	5.165
5	-6.3	15.961	17.021
6	-6.2	4.484	5.068
7	-6.2	3.462	4.488
8	-6.1	5.056	7.575
9	-6.1	5.702	7.261

Table 2

Geometrical parameters of the title compound (DFT/XRD)Bond lengths (Å)

C11-C8	1.7601/1.7322	O2-C11	1.2135/1.2143
N3-C5	1.4704/1.4712	N3-C9	1.4138/1.4183
N3-C11	1.3989 /1.3803	N4-C8	1.3160/1.3223
N4-C14	1.3434/1.3383	C5-C7	1.4969/1.4883
C5-H20	1.0951/0.9700	C5-H22	1.0949/0.9700
C6-C7	1.3843/1.3763	C6-C11	1.4904/1.4813
C6-C15	1.3892/1.3823	C7-C8	1.3901/1.3783
C9-C10	1.4044/1.3873	C9-C12	1.4059/1.3963
C10-C16	1.3845/1.3803	C10-H21	1.0802/0.9300
C12-C18	1.3910/1.3833	C12-H23	1.0771/0.9300
F13-C16	1.3557/1.3603	C14-C15	1.3924/1.3783
C14-H26	1.0845/0.9300	C15-H25	1.0821/0.9300
C16-C17	1.3831/1.3634	C17-C18	1.3936/1.3734
C17-H24	1.0818/0.9300	C18-H19	1.0835/0.9300

Bond angles (°)

C5-N3-C9	121.2/120.7	C5-N3-C11	112.3/112.5
C9-N3-C11	126.6/126.7	C8-N4-C14	118.6/116.9
N3-C5-C7	103.0/102.3	N3-C5-H20	111.1/111.3
N3-C5-H22	111.1/111.3	C7-C5-H20	111.8/111.3
C7-C5-H22	111.9/111.3	H20-C5-H22	108.0/109.2
C7-C6-C11	109.2/108.7	C7-C6-C15	121.0/120.9
C11-C6-C15	129.9/130.4	C5-C7-C6	109.9/110.5
C5-C7-C8	132.5/132.2	C6-C7-C8	117.6/117.4
C11-C8-N4	117.6/117.1	C11-C8-C7	119.4/118.9
N4-C8-C7	123.0/124.0	N3-C9-C10	118.9/118.4
N3-C9-C12	122.0/122.3	C10-C9-C12	119.1/119.3
C9-C10-C16	119.1/118.8	C9-C10-H21	122.8/120.6
C16-C10-H21	118.1/120.6	O2-C11-N3	127.8/127.6

O2-C11-C6	126.6/126.3	N3-C11-C6	105.7/106.0
C9-C12-C18	119.7/119.2	C9-C12-H23	119.8/120.4
C18-C12-H23	120.5/120.4	N4-C14-C15	123.7 /124.7
N4-C14-H26	115.5/117.7	C15-C14-H26	120.8/117.7
C6-C15-C14	116.1/116.2	C6-C15-H25	121.8/121.9
C14-C15-H25	122.1/121.9	C10-C16-F13	117.8/116.7
C10-C16-C17	123.1/123.3	F13-C16-C17	119.1/119.9
C16-C17-C18	117.2/117.2	C16-C17-H24	120.4/121.4
C18-C17-H24	122.4/121.4	C12-C18-C17	121.9/122.2
C12-C18-H19	118.8/118.9	C17-C18-H19	119.3/118.9

Dihedral angles (°)

C7-C5-N3-C9	179.1/-179.8	C7-C5-N3-C11	0.3/ 0.1
C10-C9-N3-C5	-2.8/ -0.6	C12-C9-N3-C5	176.7/179.3
C10-C9-N3-C11	175.9/179.5	C12-C9-N3-C11	-4.6/-0.5
O2-C11-N3-C5	-179.8/179.9	C6-C11-N3-C5	-0.1/-0.0
O2-C11-N3-C9	1.5/-0.1	C6-C11-N3-C9	-178.8/179.9
C11-C8-N4-C14	-179.9/180.0	C7-C8-N4-C14	-0.7/-0.0
C15-C14-N4-C8	0.8/-0.0	C6-C7-C5-N3	-0.5/-0.1
C8-C7-C5-N3	178.5/180.0	C11-C6-C7-C5	0.5/0.1
C11-C6-C7-C8	178.7/ 180.0	C15-C6-C7-C5	-179.6/-179.9
C15-C6-C7-C8	1.3/-0.0	C7-C6-C11-O2	-179.5/-180.0
C7-C6-C11-N3	-0.2/ -0.0	C15-C6-C11-O2	-0.4/ -0.0
C15-C6-C11-N3	179.9/ 180.0	C14-C15-C6-C7	-1.1/-0.0
C14-C15-C6-C11	178.8/ 180.0	C11-C8-C7-C5	0.1/-0.1
N4-C8-C7-C5	-179.2/179.9	C11-C8-C7-C6	178.9/180.0
N4-C8-C7-C6	-0.3/0.1	N3-C9-C10-C16	179.1/180.0
C12-C9-C10-C16	-0.4/-0.0	N3-C9-C12-C18	-179.2/-180.0
C10-C9-C12-C18	0.3/-0.0	C9-C10-C16-F13	-177.3/-180.0
C9-C10-C16-C17	0.4/0.0	C17-C18-C12-C9	-0.2/0.0
N4-C14-C15-C6	0.0/0.0	C10-C16-C17-C18	-0.2/-0.0
F13-C16-C17-C18	177.4/180.0	C16-C17-C18-C12	0.1/0.0

Table 3

Calculated scaled wavenumbers, observed IR, Raman bands and vibrational assignments of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

B3LYP/6-311++G(d,p)			IR	Raman	Assignments ^a
$\nu(\text{cm}^{-1})$	IR _I	R _A	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3132	9.46	36.86	3122	3122	$\nu\text{CHIII}(99)$
3101	0.41	45.85	-	-	$\nu\text{CHIII}(99)$
3088	2.92	152.68	3086	3087	$\nu\text{CHI}(95)$
3088	1.37	188.93	3086	3087	$\nu\text{CHIII}(99)$
3061	8.10	102.26	-	3065	$\nu\text{CHIII}(99)$
3053	13.51	181.97	3020	3051	$\nu\text{CHI}(95)$
2942	4.59	53.14	2955	2935	$\nu\text{CH}_2(100)$
2911	8.09	115.60	2915	2909	$\nu\text{CH}_2(100)$
1701	350.34	122.23	1708	1968	$\nu\text{C=O}(77)$
1587	155.31	254.14	1586	1600	$\delta\text{CHIII}(10), \nu\text{PhIII}(56)$
1578	16.24	173.19	-	-	$\nu\text{PhI}(56)$
1560	97.53	1.94	-	1562	$\nu\text{PhIII}(64), \delta\text{CHIII}(19)$
1551	72.92	66.62	-	1540	$\nu\text{PhI}(73), \delta\text{CHI}(13)$
1463	127.09	31.20	1461	-	$\delta\text{CHIII}(17), \nu\text{PhIII}(47)$
1441	63.28	68.30	1444	1450	$\delta\text{CH}_2(82)$
1427	25.77	93.51	-	-	$\delta\text{CHIII}(24), \nu\text{PhIII}(44)$
1417	8.04	17.32	1415	-	$\delta\text{CHI}(16), \nu\text{PhI}(42)$
1387	72.17	6.81	1382	-	$\nu\text{PhI}(46), \nu\text{CC}(17), \delta\text{CHI}(22)$
1336	222.30	532.81	-	-	$\delta\text{CH}_2(35), \nu\text{CN}(33)$
1294	32.48	32.83	1301	1302	$\nu\text{PhIII}(62), \delta\text{CHIII}(32)$
1279	35.13	126.55	1277	1275	$\nu\text{CN}(42), \delta\text{CHIII}(39)$
1263	14.95	19.86	-	-	$\nu\text{PhI}(43), \nu\text{PhIII}(12)$
1247	59.33	119.02	-	1244	$\nu\text{PhI}(31), \delta\text{CH}_2(13), \delta\text{CHI}(12)$
1232	41.25	80.78	1235	-	$\nu\text{CF}(46), \delta\text{CHI}(13)$
1178	73.56	28.67	1176	-	$\delta\text{CHI}(43), \nu\text{CC}(17), \nu\text{PhI}(18)$
1164	74.45	7.63	1162	-	$\delta\text{CHIII}(47), \delta\text{CH}_2(11)$

1164	10.57	4.39	1162	-	$\delta\text{CH}_2(84)$
1146	97.66	32.41	1147	1150	$\delta\text{PhI}(41)$, $\nu\text{PhII}(12)$, $\nu\text{CCII}(10)$
1138	82.06	7.36	-	-	$\delta\text{CHIII}(58)$, $\nu\text{CF}(12)$
1119	17.30	15.33	-	1119	$\nu\text{CNII}(56)$
1064	22.03	1.78	1060	1060	$\delta\text{CHIII}(34)$, $\nu\text{PhIII}(25)$
1039	17.57	3.80	-	-	$\nu\text{CNII}(13)$, $\delta\text{CHIII}(19)$, $\nu\text{PhIII}(18)$
1036	6.92	16.91	-	1030	$\delta\text{CHI}(44)$, $\nu\text{PhI}(17)$, $\nu\text{CNI}(21)$
978	0.34	0.26	980	980	$\delta\text{CH}_2(80)$
974	1.45	84.00	970	970	$\delta\text{PhIII}(24)$, $\nu\text{PhIII}(41)$
955	0.88	0.20	-	-	$\gamma\text{CHIII}(78)$
954	0.13	0.11	952	-	$\gamma\text{CHI}(81)$
937	7.28	21.15	930	938	$\nu\text{CF}(19)$, $\delta\text{C=O}(22)$, $\nu\text{PhIII}(25)$
874	0.49	0.15	877	872	$\gamma\text{CHIII}(86)$
837	17.32	0.40	840	835	$\gamma\text{CHI}(84)$
837	72.68	31.11	840	835	$\delta\text{PhI}(22)$, $\nu\text{PhII}(11)$, $\nu\text{CCl}(11)$
826	14.30	20.55	-	-	$\delta\text{PhI}(43)$, $\nu\text{CCII}(27)$
818	42.47	0.15	-	-	$\gamma\text{CHIII}(53)$, $\tau\text{PhIII}(23)$
762	38.63	0.46	764	-	$\gamma\text{CHIII}(77)$
742	6.61	0.24	744	744	$\tau\text{PhI}(32)$, $\gamma\text{C=O}(30)$, $\tau\text{PhII}(17)$
724	23.97	20.84	726	725	$\delta\text{PhII}(38)$, $\delta\text{PhIII}(37)$
706	2.71	8.36	706	706	$\delta\text{PhII}(23)$, $\delta\text{PhI}(12)$, $\delta\text{C=O}(39)$, $\nu\text{CNII}(16)$
690	6.30	1.04	688	-	$\tau\text{PhI}(49)$, $\delta\text{CCl}(21)$, $\gamma\text{C=O}(14)$
666	18.51	0.15	-	670	$\tau\text{PhIII}(16)$, $\nu\text{CCl}(42)$
621	8.58	6.63	625	625	$\delta\text{PhIII}(43)$, $\delta\text{PhII}(11)$, $\delta\text{C=O}(15)$, $\delta\text{PhI}(11)$
594	12.62	3.45	-	600	$\delta\text{PhI}(34)$, $\delta\text{CN}(10)$
589	0.24	1.43	-	-	$\gamma\text{CF}(39)$, $\gamma\text{CN}(25)$, $\tau\text{PhIII}(29)$
534	15.75	2.47	-	531	$\delta\text{PhII}(37)$, $\delta\text{PhI}(22)$
508	7.16	4.22	-	-	$\delta\text{PhIII}(71)$
505	0.04	0.19	-	-	$\delta\text{CCl}(33)$, $\tau\text{PhI}(41)$

480	0.85	0.13	-	-	τ PhI(61), τ PhII(18)
446	2.64	1.12	-	-	δ CF(50), δ CN(25)
442	3.30	0.09	-	-	τ PhIII(57), γ CF(13)
395	4.83	6.88	-	-	δ PhI(33), δ CCl(11)
329	4.97	1.03	-	335	δ CCl(23), δ CN(10)
310	3.62	2.36	-	315	δ C=O(24), δ CN(33)
285	0.22	0.05	-	-	γ CN(36), τ PhIII(27), τ PhII(16)
259	5.86	0.58	-	-	τ C=C(31), τ PhII(38), δ CCl(11), τ PhI(16)
254	0.29	2.50	-	248	δ CN(21), δ CF(12), τ PhIII(22), τ PhI(13)
228	0.18	1.61	-	225	τ PhIII(68), τ PhII(19)
192	2.31	0.62	-	194	τ PhI(42), τ PhII(29)
186	3.37	1.55	-	184	δ CCl(41), δ CN(23)
153	1.63	4.48	-	-	τ C=C(21), τ PhII(23), τ PhIII(16), γ CN(12)
92	5.22	0.32	-	90	τ PhI(30), τ PhII(31)
87	0.06	0.88	-	-	δ CN(45), δ CCl(13)
46	0.02	0.80	-	-	γ CN(53), τ II(15), τ C=C(11)
24	0.66	1.33	-	-	τ CN(77)

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; PhI-C6-C7-C8-N4-C14-C15 ring; PhII-C7-C6-C11-N3-C5 ring; PhIII-C9-C10-C16-C17-C18-C12 ring.

Table 4

Experimental and calculated ^1H and ^{13}C NMR chemical shifts (ppm) of title compound.

^{13}C -NMR

Atom	Experimental (ppm)	TMS B3LYP/6-311+G(2d,p) GIAO (ppm)
5C	49.47	51.56
6C	145.38	149.77
7C	134.85	138.53
8C	149.98	160.08
9C	140.14	147.92
10C	106.74	105.88
11C	164.40	169.28
12C	117.15	118.91
14C	143.02	155.23
15C	115.59	120.76
16C	161.02	172.31
17C	111.85	115.12
18C	130.10	135.90

^1H -NMR

H19	7.46-7.51	7.51
H20	5.09	4.63
H21	7.89	6.67
H22	5.09	4.63
H23	7.73	9.33
H24	7.05	6.99
H25	7.79	7.73
H26	8.61	8.63

Table 5

Theoretical electronic absorption spectra of title compound (absorption wavelength λ (nm), excitation energies E (eV) and oscillator strengths (f)) using TD-DFT/B3LYP/6311++G(d,p) method.

Excitation	CI expansion	Energy	Wavelength	Oscillator
-	-	Coefficient (eV)	(nm)	Strength (f)
67→68	0.67597	3.8040	325.93	0.2091
64→68	0.67636	4.1087	301.76	0.0002
66→68	0.66909	4.2194	293.84	0.0049
67→70	0.12034	-	-	-
65→68	0.41730	4.3460	285.28	0.0276
67→69	0.51470	-	-	-
63→68	0.65526	4.3711	283.65	0.0018
62→69	0.16664	4.5534	272.29	0.0668
65→68	0.47768	-	-	-
67→69	0.44165	-	-	-

Table 6

Mulliken atomic charges of title compound by B3LYP/6-311++G (d,p)

<u>Atoms</u>	<u>Atomic charges</u>
C11	0.575
O2	-0.282
N3	0.133
N4	0.127
C5	-1.360
C6	0.442
C7	1.920
C8	-2.014
C9	-0.132
C10	0.343
C11	-0.493
C12	-0.044
F13	-0.162
C14	-0.269
C15	-0.017
C16	-0.314
C17	0.286
C18	-0.495
H19	0.185
H20	0.222
H21	0.234
H22	0.225
H23	0.250
H24	0.1994
H25	0.228
<u>H26</u>	<u>0.223</u>

Table 7

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	E(j)-E(i) ^b	F(i,j) ^c
C11-C8	σ	1.98708	N4-C14	σ^*	0.01617	3.15	1.22	0.055
-	-	-	C6-C7	σ^*	0.02911	2.60	1.26	0.051
O2-C11	σ	1.99326	N3-C5	σ^*	0.01987	1.11	1.38	0.035
-	-	-	N3-C11	σ^*	0.09009	1.14	1.48	0.037
-	-	-	C6-C11	σ^*	0.07174	2.15	1.49	0.051
O2-C11	π	1.97975	C6-17	π^*	0.35291	4.04	0.40	0.039
N3-C5	σ	1.98189	O2-C11	σ^*	0.01044	3.42	1.34	0.061
-	-	-	N3-C9	σ^*	0.03447	1.42	1.14	0.036
-	-	-	C7-C8	σ^*	0.04304	3.07	1.29	0.056
-	-	-	C9-C12	σ^*	0.02162	2.42	1.30	0.050
N4-C8	π	1.74146	C6-C7	π^*	0.35291	13.40	0.35	0.062
-	-	-	C14-C15	π^*	0.27073	21.79	0.34	0.078
N4-C14	σ	1.97609	C11-C8	σ^*	0.06594	5.42	0.96	0.065
-	-	-	N4-C8	σ^*	0.02838	1.54	1.37	0.041
-	-	-	C14-C15	σ^*	0.02278	1.34	1.39	0.038
C5-C7	σ	1.97048	N3-C9	σ^*	0.03447	3.25	1.07	0.053
-	-	-	N4-C8	σ^*	0.02838	2.15	1.20	0.045
-	-	-	C6-C7	σ^*	0.02911	2.48	1.21	0.049
-	-	-	C6-C11	σ^*	0.07174	0.59	1.08	0.023
-	-	-	C6-C15	σ^*	0.02199	4.08	1.22	0.063
-	-	-	C7-C8	σ^*	0.04304	3.01	1.21	0.054
C6-C7	σ	1.95512	C11-C8	σ^*	0.06594	5.29	0.084	0.060
-	-	-	O2-C11	σ^*	0.01044	2.84	1.32	0.055
-	-	-	N3-C5	σ^*	0.01987	1.12	1.01	0.030
-	-	-	C5-C7	σ^*	0.02445	2.02	1.10	0.042
-	-	-	C6-C11	σ^*	0.07174	1.20	1.13	0.033
-	-	-	C6-C15	σ^*	0.02199	5.16	1.27	0.073
-	-	-	C7-C8	σ^*	0.04304	4.58	1.26	0.068
C6-C7	π	1.63462	O2-C11	π^*	0.30641	20.66	0.29	0.070
-	-	-	N4-C8	π^*	0.42835	27.23	0.26	0.077

C6-C11	σ	1.97048	O2-C11	σ^*	0.01044	1.95	1.27	0.045
-	-	-	N3-C9	σ^*	0.03447	4.27	1.07	0.060
-	-	-	C6-C7	σ^*	0.02911	2.49	1.21	0.049
-	-	-	C6-C15	σ^*	0.02199	2.52	1.22	0.050
-	-	-	C7-C8	σ^*	0.04304	3.55	1.21	0.059
-	-	-	C14-C15	σ^*	0.02278	1.36	1.22	0.036
C9-C10	σ	1.96952	N3-C9	σ^*	0.03447	1.03	1.11	0.030
-	-	-	N3-C11	σ^*	0.09009	3.04	1.11	0.053
-	-	-	C9-C12	σ^*	0.02162	3.92	1.26	0.063
C9-C10	π	1.67472	C12-C18	π^*	0.32140	15.96	0.30	0.062
-	-	-	C16-C17	π^*	0.37854	23.74	0.29	0.075
C12-C18	π	1.67648	C9-C10	π^*	0.42039	23.47	0.26	0.072
-	-	-	C16-C17	π^*	0.37854	18.01	0.27	0.063
F13-C16	σ	1.99550	C9-C10	σ^*	0.01992	1.37	1.56	0.041
-	-	-	C17-C18	σ^*	0.01493	1.11	1.59	0.038
C14-C15	σ	1.98362	N4-C14	σ^*	0.01617	1.19	1.24	0.034
-	-	-	C6-C11	σ^*	0.07174	4.97	1.14	0.068
C14-C15	π	1.63546	N4-C8	π^*	0.42835	19.06	0.25	0.063
-	-	-	C6-C7	π^*	0.35291	23.75	0.29	0.074
C16-C17	σ	1.98031	C10-C16	σ^*	0.02513	4.25	1.29	0.066
-	-	-	C17-C18	σ^*	0.01493	2.51	1.30	0.051
C16-C17	π	1.66137	C9-C10	π^*	0.42039	17.89	0.28	0.650
-	-	-	C12-C18	π^*	0.32140	21.52	0.30	0.072
-	-	-	C16-C17	π^*	0.37854	0.79	0.29	0.014
C17-C18	σ	1.97393	C12-C18	σ^*	0.01452	2.51	1.29	0.051
-	-	-	F13-C16	σ^*	0.01522	4.67	0.96	0.060
-	-	-	C16-C17	σ^*	0.02640	2.43	1.27	0.050
LPC11	σ	1.99402	N4-C8	σ^*	0.02838	0.92	1.47	0.033
-	-	-	C7-C8	σ^*	0.04304	1.31	1.48	0.040
LPC11	π	1.96607	N4-C8	σ^*	0.02838	5.97	0.86	0.064
-	-	-	C7-C8	σ^*	0.04304	3.43	0.87	0.049
LPO2	σ	1.97790	N3-C11	σ^*	0.09009	1.66	1.09	0.039
-	-	-	C6-C11	σ^*	0.07174	2.39	1.11	0.046
LPO2	π	1.85153	N3-C11	σ^*	0.09009	28.51	0.66	0.125

-	-	-	C6-C11	σ^*	0.07174	19.12	0.68	0.103
LPN3	σ	1.63608	O2-C11	π^*	0.30641	54.92	0.28	0.112
-	-	-	C9-C10	π^*	0.42039	35.32	0.28	0.091
LPN4	σ	1.89489	C11-C8	σ^*	0.06594	5.25	0.48	0.045
-	-	-	C7-C8	σ^*	0.04304	10.07	0.90	0.086
-	-	-	C14-C15	σ^*	0.02278	8.70	0.90	0.081
LPF13	σ	1.98947	C10-C16	σ^*	0.02513	1.10	1.60	0.038
-	-	-	C16-C17	σ^*	0.02640	1.09	1.60	0.037
LPF13	π	1.97279	C10-C16	σ^*	0.02513	5.81	0.98	0.067
-	π	-	C16-C17	σ^*	0.02640	5.81	0.98	0.067

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

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

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

Table 8

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

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ C11-C8	1.98708	54.20	45.80	0.7362(sp ^{5.05})Cl+	16.46	83.05
-	-0.72914	-	-	0.6768(sp ^{3.29})C	23.27	76.52
σ O2-C11	1.99326	64.14	35.86	0.8008(sp ^{1.44})O+	41.00	58.87
-	-1.09877	-	-	0.5989(sp ^{1.93})C	34.09	65.77
π O2-C11	1.97975	69.62	30.38	0.8344(sp ^{1.00})O+	0.00	99.88
-	-0.39851	-	-	0.5512(sp ^{1.00})C	0.00	99.59
σ N3-C5	1.98189	63.07	36.93	0.7942(sp ^{2.31})N+	30.16	69.82
-	-0.75587	-	-	0.6077(sp ^{3.58})C	21.81	78.04
π N4-C8	1.74146	56.39	43.61	0.7509(sp ^{1.00})N+	0.00	99.85
-	-0.35062	-	-	0.6604(sp ^{1.00})C	0.00	99.89
σ N4-C14	1.97609	59.98	40.02	0.7745(sp ^{1.82})N+	35.40	64.52
-	-0.85061	-	-	0.6326(sp ^{2.19})C	31.29	68.61
σ C5-C7	1.97048	48.81	51.19	0.6987(sp ^{2.47})C+	28.83	71.11
-	-0.68125	-	-	0.7155(sp ^{2.20})C	31.23	68.75
σ C6-C7	1.95512	49.07	50.93	0.7005(sp ^{2.03})C+	32.95	66.98
-	-0.73344	-	-	0.7136(sp ^{2.08})C	32.49	67.49
π C6-C7	1.63462	49.27	50.73	0.7019(sp ^{1.00})C+	0.00	99.95
-	-0.29850	-	-	0.7122(sp ^{1.00})C	0.00	99.95
σ C6-C11	1.97048	51.92	48.08	0.7206(sp ^{2.37})C+	29.66	70.27
-	-0.68245	-	-	0.6934(sp ^{1.80})C	35.66	64.30
σ C9-C10	1.96952	50.55	49.55	0.7110(sp ^{1.80})C+	35.68	64.29
-	-0.72506	-	-	0.7032(sp ^{1.82})C	35.50	64.46
π C9-C10	1.67472	46.72	53.28	0.6835(sp ^{1.00})C+	0.00	99.96
-	-0.28229	-	-	0.7300(sp ^{1.00})C	0.00	99.95
π C12-C18	1.67648	51.66	48.34	0.7188(sp ^{1.00})C+	0.00	99.95
-	-0.26600	-	-	0.6953(sp ^{1.00})C	0.00	99.95
σ F13-C16	1.99550	72.67	27.33	0.8525(sp ^{2.34})F+	29.96	69.96
-	-1.02369	-	-	0.5228(sp ^{3.58})C	21.77	77.90
σ C14-C15	1.98362	49.07	50.93	0.7005(sp ^{1.57})C+	38.93	61.02
-	-0.74294	-	-	0.7136(sp ^{1.88})C	34.73	65.23
π C14-C15	1.63546	48.10	51.90	0.6935(sp ^{1.00})C+	0.00	99.94

-	-0.29054	-	-	0.7204(sp ^{1.00})C	0.00	99.94
σ C16-C17	1.98031	50.17	49.83	0.7083(sp ^{1.54})C+	39.92	60.68
-	-0.73497	-	-	0.7059(sp ^{1.96})C	33.79	66.15
π C16-C17	1.66137	47.67	52.33	0.6904(sp ^{1.00})C+	0.00	99.95
-	-0.28240	-	-	0.7234(sp ^{1.00})C	0.00	99.94
σ C17-C18	1.97393	50.53	49.47	0.7109(sp ^{1.77})C+	36.12	63.83
-	-0.71579	-	-	0.7033(sp ^{1.82})C	35.47	64.48
σ LPC11	1.99402	-	-	sp ^{0.20}	83.20	16.79
-	-0.94681	-	-	-	-	-
π LPC11	1.96607	-	-	sp ^{99.99}	0.47	99.99
-	-0.94681	-	-	-	-	-
σ LPO2	1.97790	-	-	sp ^{0.69}	59.01	40.97
-	-0.71045	-	-	-	-	-
π LPO2	1.85153	-	-	sp ^{99.99}	0.02	99.90
-	-0.27970	-	-	-	-	-
σ LPN3	1.63608	-	-	sp ^{1.00}	0.00	99.99
-	-0.28680	-	-	-	-	-
σ LPN4	1.89489	-	-	sp ^{2.62}	27.57	72.34
-	-0.36920	-	-	-	-	-
σ LPF13	1.98947	-	-	sp ^{0.43}	70.04	29.95
-	-1.04894	-	-	-	-	-
π LPF13	1.97279	-	-	sp ^{1.00}	0.00	99.97
-	-0.42890	-	-	-	-	-

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

Table 9

Thermo dynamical parameters of titlecompound by B3LYP/6-311++G (d,p).

parameters	Values at (Temperature 298.15k, Pressure 1 atm)
SCF energy (a.u)	: -1245.21770801
Dipole Moment (Debye)	: 0.6087
Zero-point vibrational energy (kcal mol ⁻¹)	: 116.03373
Rotational constants (GHZ)	: 0.74226 0.21200 0.16507
Entropy (cal mol ⁻¹ k ⁻¹) :	
Total	: 120.103
Translational	: 42.589
Rotational	: 33.781
Vibrational	: 43.732
Total energy (thermal), E_{total} (kcal mol ⁻¹)	
Total	: 124.725
Translational	: 0.889
Rotational	: 0.889
Vibrational	: 122.948

Thermodynamic properties at different temperatures at the B3LYP/6-311++G (d,p) level for title compound.

Temperature (K)	S (J mol ⁻¹ k ⁻¹)	Cp (J mol ⁻¹ k ⁻¹)	ΔH (kJ mol ⁻¹)
100	336.72	95.72	6.30
200	423.93	164.39	19.27
298.15	502.62	234.30	38.84
300	504.07	235.59	39.28
400	581.08	301.34	66.20
500	654.42	356.10	99.17
600	723.36	399.76	137.05
700	787.68	434.38	178.82
800	847.56	462.13	223.70

900	903.34	484.71	271.08
<u>1000</u>	<u>955.41</u>	<u>503.33</u>	<u>320.51</u>

Fig.1 Optimized geometry of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

Hirshfeld surfaces for title compound A) d_{norm} B) shape index and C) curvedness.

Hirshfeld surfaces mapped with d_{norm} showing the C8–C11...C11ⁱ intermolecular interactions.

Fingerprint plot of title compound; a) total Hirshfeld surface area b) H...H, b) H...C, c) H...Cl, d) H...F, e) H...O and f) H...N interactions showing the percentage of contacts

created to the total Hirshfeld surface area of the molecules. d_e , the distance from the point to the nearest nucleus exterior to the surface, and d_i , the distance to the nearest nucleus interior to the surface, are defined.

Fig. 2 Hirshfeld surfaces

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205.59 ALIE [kcal/mol] 368.32

Fig.3 ALIE surface of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo [3,4-c]pyridin-1-one molecule

Fig.4 Fukui functions a) f^+ and b) f^- of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one molecule

Fig.5 BDEs of all single acyclic bonds of 4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one molecule

Fig.6 RDFs of atoms of of4-chloro-2-(3-fluorophenyl)-2,3-dihydro-1H-pyrrolo [3,4-c]pyridin-1-one molecule with significant interactions with water molecules

Fig.7 The ligand interaction with the amino acids of human $\alpha 9$ nicotinic acetylcholine receptor antagonist

Highlights

- Single crystal XRD, IR, Raman spectra were studied
- Most reactive sites are predicted by using MEP plot
- BDEs are calculated to investigate autoxidation and degradation properties
- A lead compound for developing new anti-cancerous drug