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Synthesis, crystal structure analysis, spectral investigations, DFT computations and molecular dynamics and docking study of 4-benzyl-5-oxomorpholine-3-carbamide, a potential bioactive agent

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Abstract

4-benzyl-5-oxomorpholine-3-carbamide has been synthesized; single crystals were grown by slow evaporation solution growth technique at room temperature and characterized by single crystal X-ray diffraction, FT-IR, FT-Raman and ¹H-NMR. The compound crystallizes in the monoclinic space group $P2_1/n$. The molecular geometry of the compound was optimized by using Density Functional Theory (DFT/B3LYP) method with 6-311++G(d,p) basis set in the ground state and geometric parameters are in agreement with the X-ray analysis results of the structure. The experimental vibrational spectra were compared with the calculated spectra and each vibrational wave number was assigned on the basis of potential energy distribution (PED).

The electronic and charge transfer properties have been explained on the basis of highest occupied molecular orbital's (HOMOs) and lowest unoccupied molecular orbital's (LUMOs). Besides molecular electrostatic potential (MEP), frontier molecular orbital's (FMOs), some global reactivity descriptors, thermodynamic properties, non-linear optical (NLO) behavior and Mulliken charge analysis of the title compound were computed with the same method in gas phase, theoretically. Potential reactive sites of the title compound have been identified by average local ionization energy and Fukui functions, both mapped to the electron density surface. Bond dissociation energies for all single acyclic bonds have been calculated in order to investigate autoxidation and degradation properties of the title compound. Atoms with pronounced interactions with water molecules have been detected by calculations of radial distribution functions after molecular dynamics simulations. The experimental results are compared with the theoretical calculations using DFT methods for the fortification of the paper. Further the docking studies revealed that the title compound as a docked ligand forms a stable complex with pyrrole inhibitor with a binding affinity value of -7.5kcal/mol. This suggests that the title compound might exhibit inhibitory activity against pyrrole inhibitor. To confirm the potential practical applicability of the title compound antimicrobial activity was tested against gram negative and gram positive bacteria.

Keywords: Oxomorpholine; XRD; ALIE; RDF; BDE; Molecular Docking.

1. Introduction

Morpholines are common structural cores of a broad range of biological and pharmacological natural or synthetically important organic molecules [1]. Morpholine is an organic compound which is considered as an important building block in the field of medicinal chemistry. Human Epidermal Growth Factor Receptor kinase inhibitors, glucosidase inhibitors, P38 MAP kinase inhibitors, PI3K kinase inhibitors (used in tumor chemotherapy), phosphoinositide 3-kinase inhibitors, FLT3 (thirotine) kinase inhibitors, urease inhibitors, cysteine protease inhibitors, selective SV2 receptor agonists, D-dopamine receptor agonists, 5-lipoxygenase inhibitors, V3 vasopressin receptor antagonists, σ receptor antagonists, nicotine acetylcholine receptor antagonist human cancer cell growth inhibitors were described [2-4]. Micheli et al. [5] reported a new series of morpholine derivatives as selective DAD3 receptor antagonists and their in vitro profile and pharmacokinetic data. Of the various nitrogen heterocycles, morpholine derivatives are of particular importance in naturally occurring and

biologically active molecules have anti-inflammatory and antagonist properties and used as chiral auxiliary in some chemical transformations [6]. Hamidian and Azizi [7] reported the synthesis of novel compounds containing morpholine and 5(4H)-oxazolone rings as potent tyrosinase inhibitors. An investigation of the aromatic substitution on antihyperlipidemic morpholine derivatives with antioxidant activity is reported in literature [8]. In addition to pharmacological properties, morpholines are widely used in organic synthesis, however their uses is most frequently restricted to application as simple bases, N-alkylating agent, catalysts, and chiral auxiliaries [9-15]. Thus, up to now, numerous strategies toward the synthesis of substituted morpholines have been reported [16-25]. Despite these advances, the synthetic approach to substituted morpholine is still scarce. The present work discusses with synthesis, crystal structure analysis, vibrational assignments, natural bond orbital analysis, molecular frontier orbital analysis, nonlinear optical properties and molecular potential surface study of the title compound. Besides, theoretical and experimental studies were carried out to provide a complete description of molecular structure and vibrational spectral studies of the title compound. In addition, molecular docking study of the title compound is also presented in view of the diverse biological activities of morpholine derivatives.

Biologically active molecules are used in pharmaceutical care products. These compounds are synthesized to be stable in water in order to fulfill their primary role, but eventually they are accumulated in environment. So far biologically active molecules have been detected in all types of water and it is needed to develop efficient and economical methods for their removal [26-28]. Degradation of these compounds under natural conditions is slow and consequently even molecules with lower stability are considered to be pseudo-persistent, as they continuously enter the environment. Advanced oxidation processes are seen as effective alternative to conventional purification methods, which are useless for the degradation of mentioned molecules [29]. Principles of molecular modeling allow scientists to rationalize their efforts in this field because some degradation properties can be predicted after DFT calculations and molecular dynamics (MD) simulations, which have been done in this work as well. Namely, in order to predict oxidation and degradation properties we have calculated bond dissociation energies (BDE) for all single acyclic bonds, while calculations of radial distribution functions (RDF) provided us with information which atoms of the title molecule have significant interactions with water.

2. Experimental and computational methods

2.1 General remarks

The reagents and solvents used for synthesis were of Analar grade and used without further purification. The synthesis was carried out under oxygen free inert atmosphere. ^1H -NMR spectra were recorded on Bucker 400MHz spectrometer operating at room temperature in DMSO-d_6 as solvent. The chemical shifts values (δ) are reported in parts per million (ppm) using TMS as an internal standard. FT-IR spectrum (Fig.1) was recorded in the range $4000\text{--}400\text{ cm}^{-1}$ region with an ATR module ALPHA-T Bruker FT-IR spectrophotometer. Raman spectroscopy measurements (Fig. 2) on solid compound were carried out using Bruker RFS 100/s, Germany. All the experiments were performed using the excitation wavelength of 1064 nm of an Nd:YAG laser and the spectral resolution was 2 cm^{-1} .

2.2 Preparation of 4-benzyl-5-oxomorpholine-3-carbamide

To a stirred solution of 4-benzyl-5-oxomorpholine-3-carboxylic acid (1.0g, 4.25 mmol) in DCM (15 mL) at 0°C , was added oxalylchloride (0.91 mL, 10.62 mmol), DMF (catalytic amount). The reaction mixture was later brought to room temperature and allowed to stir at room temperature for 2 hours. The reaction mixture was evaporated under vacuum to remove volatiles and re-dissolved in THF (15 mL). The reaction mixture was cooled to 0°C , added excess liquor ammonia and stirred at room temperature for 1 hour. Resulting solid was filtered and washed with minimum water, dried under vacuum to afford 4-benzyl-5-xomorpholine-3-carbamide (0.488 g, 49%) as a white solid (Scheme 1).

2.3 X-ray crystallography

A suitable prism like crystal was selected and mounted on a Bruker APEX-II CCD diffractometer using graphite mono-chromated $\text{MoK}\alpha$ ($\lambda=0.71073\text{ \AA}$) radiation and detector (CCD). The crystal was kept at 298(2) K during data collection. The structure was solved using Olex2 software [30] with the olex2.solve [31] structure solution program using Charge Flipping and the structure was refined with the ShelXL [32] refinement package using Least Squares minimization. All the non-hydrogen atoms were revealed in the first difference Fourier map itself and were refined anisotropically. All the hydrogen atoms were positioned geometrically. All H atoms were positioned geometrically, with $\text{C-H} = 0.97\text{ \AA}$ for methylene H, $\text{C-H} = 0.98\text{ \AA}$ for methane H, $\text{C-H} = 0.93\text{ \AA}$ for aromatic H, and refined using a riding model with $\text{Uiso(H)} = 1.2\text{Ueq(C)}$ for all H atoms. The amino H atoms were located in a difference map and were refined freely.

2.4 Computational details

All calculations of the title compound were performed in the ground state by using Gaussian09 software [33] at DFT/B3LYP method with the 6-311++G(d,p) (5D, 7F) basis set and the visualizations of the results/optimized geometry was achieved through GaussView [34]. The calculated wave numbers are scaled by a scaling factor of 0.9613 to obtain a better agreement with the experimental results [35]. The calculated wavenumbers were assigned by means of the potential energy distribution (PED) using GAR2PED program [36]. Theoretical ^1H -NMR chemical shifts were calculated in ground state by using GIAO approach and chemical shifts were calculated with reference to TMS. In addition, Mullikan charges, chemical reactivity descriptors, frontier molecular orbital energy (HOMO-LUMO) and molecular electrostatic potential (MEP) were carried out with same method. ALIE surfaces, Fukui functions and BDE have been calculated with Jaguar 9.0 [37] program as implemented in Schrödinger Materials Science Suite 2015-4 [38]. DFT/B3LYP level of theory, with 6-311++G(d,p), 6-31+G(d) and 6-311G(d,p) basis sets, has been used respectively. Intra-molecular non-covalent interactions have been investigated using the method of Johnson [39, 40].

MD simulations have been conducted with Desmond [41-44] program, as implemented in Schrödinger Materials Science Suite 2015-4 [38]. OPLS 2005 [45] force field with NPT ensemble class have been used, while pressure and temperature were set to 1.0325 bar and 300 K, respectively. Besides, simulation time was 5 ns with cut-off radius of 12 Å. System was modeled in such way that one molecule of title compound was placed in cubic box with ~3000 water molecules. Simple point charge (SPC) model [46] was used for the description of solvent.

2.5 Hirshfeld Surfaces Analysis

We examined the intermolecular interactions present in title compound using Hirshfeld surface analysis, which is a useful tool to describe the surface characteristics of molecules [47, 48]. Hirshfeld surfaces [49, 50] and the associated 2D fingerprint plots [51-53] are unique for any crystal structure, provide a quantitative measure of the intermolecular interactions on the surface [49, 54] calculated by using Crystal Explorer [55] and which accepts a structure input file in the CIF format. For each point on the Hirshfeld isosurface, 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. The normalized contact distance (d_{norm}) based on d_e and d_i is given by

$$dnorm = \frac{(di - r_{vdW})}{r_{vdW}} + \frac{(de - r_{vdW})}{r_{vdW}}$$

Where, r_i^{vdW} and r_e^{vdW} are the van der Waals radii of atoms. In the color scale, negative sign values of d_{norm} are visualized by the red color, indicating contacts shorter than the sum of van der Waals radii. The white color denotes intermolecular distances close to van der Waals contacts with d_{norm} values equal to zero. In turn, contacts longer than the sum of vander Waals radii represent with values of positive sign d_{norm} are colored with blue. The Hirshfeld surfaces of title compound illustrated in Fig.3a, showing surfaces that have been mapped over a $d_{norm}(A)$, shape index (B) and curvedness (C) range of -0.537 to 1.313 Å, -1.0 to 1.0 Å and -4.0 to 0.4 Å. The dominant interactions between the carbamide N-H and the O of carbamide and O of oxo group can be seen in the Hirshfeld surfaces as the bright red areas marked as a, b, c and d in Fig. 3b. The light red spots labeled as e are due to C-H...O interactions (Fig. 3b). In the 2D fingerprint plots (Fig. 3c), the N-H...O intermolecular interactions appear as two distinct spikes labeled as a and b. Prominent pairs of sharp spikes of almost equal lengths in the fingerprint plots (Fig. 3c) are characteristics of nearly equal N(donor)...O(acceptor) distances and a cyclic hydrogen-bonded $R_m^n(X)$ synthon. The upper spike a (Fig. 3b) corresponds to the donor spike (H atom in CONH₂ group interacting with O-atoms of the CONH₂ group and O-atom of the C=O), with the lower spike b being an acceptor spike (O-atoms of the CONH₂ group and O-atom of the C=O interacting with H- atom of CONH₂-groups). The wings marked in Fig. 3c (encircled in red) are due to the C...H contacts. A significant difference in terms of H...H contacts appears as spikes (marked as black circles in Fig. 3c). The relative contribution of the different interactions to the Hirshfeld surface was calculated for title compound. It is evident that the H...H contacts can account for about 54.2% of the Hirshfeld surface area; The remaining contribution was mostly due to H-O 30.4%, H-C 12.5% interactions, with only minor contribution from N-H, N-N, C-C, C-O and O-O (maximum 3.9%).

3. Results and discussion

3.1. Crystal structural analysis

The title compound crystallizes in monoclinic $P2_1/n$ with $a = 9.9125 \text{ \AA}$, $b = 10.3715 \text{ \AA}$, $c = 11.6326 \text{ \AA}$, $V = 1168.0 \text{ \AA}^3$ and $Z = 4$. The ORTEP diagram of the compound with optimized geometry is given in Fig. 4 and the packing of molecules in the crystal lattice are shown in Fig.5 [56]. The crystallographic data and refinement parameters are summarized in table 1. The

crystal structure of the compound features two strong hydrogen bonds involving the amide group, namely, N1-H31...O3 and N1-H30...O29, which form inversion related $R_2^2(8)$ and $R_2^2(14)$ dimmers respectively. These alternating dimmers propagate along the [010] axis resulting in the formation of 1D ribbons along [010] (Fig. 5a). The chains with second level graph set notation $C_2^2(11)$ is realized from the 1D ribbons of alternating N-H...O dimmers (Fig.5a). In addition to this, C26-H28...O3 interactions link the molecules into 1D $C_1^1(5)$ chains (Fig.5b), and thus resulting in a two dimensional architecture (Fig.5c). The geometric parameters for hydrogen bonds and other intermolecular contacts are listed in table 2.

3.2 Geometrical parameters

The optimized geometrical (Fig.4) parameters with XRD data are given in Table 3. The C-C bond lengths (DFT/XRD) in the phenyl ring of the title compound are in range 1.3919-1.4012/1.3563-1.3802 Å and for benzene the C-C bond length is 1.3993 Å [57]. For the title compound, the C-N bond lengths (DFT/XRD) $C_8-N_7 = 1.4774/1.4667$ Å, $C_5-N_7 = 1.4665/1.4658$ Å, $C_{22}-N_7 = 1.3713/1.3448$ Å, $C_4-N_1 = 1.3580/1.3122$ Å. The C-N bond lengths $C_{22}-N_7$ and C_4-N_1 are much shorter than the normal C-N bond length of 1.49 Å [58] which confirms these bonds to have some character of a double or conjugated bond [59]. The C=O bond lengths (DFT/XRD) $C_4-O_3 = 1.2181/1.2324$ Å, $C_{22}-O_{29} = 1.2229/1.2308$ Å and C-O bond lengths (DFT/XRD) $C_{25}-O_2 = 1.4181/1.4174$ Å, $C_{23}-O_2 = 1.4157/1.4128$ Å which are in agreement with the reported values [60]. At C_{22} position the bond angles are, $C_{23}-C_{22}-N_7 = 117.2/118.2^\circ$, $C_{23}-C_{22}-O_{29} = 119.4/118.7^\circ$, $N_7-C_{22}-O_{29} = 123.4/123.1^\circ$ and the asymmetry in these angles reveals the interaction between carbonyl group and the neighboring units. At C_4 position the bond angles are, $N_1-C_4-O_3 = 123.6/123.4^\circ$, $N_1-C_4-C_5 = 116.9/118.8^\circ$, $C_5-C_4-O_3 = 119.5/117.8^\circ$ which reveals the interaction between carbonyl and NH_2 groups. The two rings in the title molecule are tilted from each other as is evident from the torsion angles, $C_5-N_7-C_8-C_{11} = -73.1^\circ$, $C_{22}-N_7-C_8-C_{11} = 99.5^\circ$, $C_{20}-C_{11}-C_8-N_7 = -70.3^\circ$, $C_{12}-C_{11}-C_8-N_7 = 109.9^\circ$.

3.3 IR and Raman spectra

The calculated (scaled) wavenumbers, observed IR, Raman bands and assignments are given in table 4. The phenyl and oxomorpholine rings are designated as PhI and PhII in the following discussion. The C=O stretching mode is observed in the region 1850-1550 cm^{-1} [61] and in the present case the carbonyl stretching modes are observed at 1694, 1648 cm^{-1} in the IR spectrum, 1691, 1660 cm^{-1} in the Raman spectrum and corresponding theoretical values are,

1694, 1655 cm^{-1} with high IR intensities and moderate Raman activities and with a PED of 74 and 78%. The deformation modes of C=O are expected in the regions, 625 ± 70 and 540 ± 80 cm^{-1} [62]. The C=O deformation modes are reported at 798 cm^{-1} in the IR spectrum, 797, 558, 535 cm^{-1} in the Raman spectrum and at 799, 711, 561, 530 cm^{-1} theoretically [63]. The C-O-C stretching modes are expected in the region 1200-850 cm^{-1} [62, 64] and for the title compound these modes are assigned at 1105, 922 cm^{-1} in the IR spectrum, 1113, 925 cm^{-1} in the Raman spectrum and at 1108, 921 cm^{-1} theoretically with IR intensities, 76.67, 30.01 and the Raman activities are low. For the mode at 921 cm^{-1} , the PED contribution is 35% which is mixed mode while the mode at 1108 cm^{-1} has a PED of 60%. Mary et al. reported the C-O-C stretching vibrations at 1101, 1099 cm^{-1} experimentally and at 1102, 942, 940 cm^{-1} theoretically [65, 66].

The vibration modes associated with NH_2 group are expected in the regions, 3360-3540 cm^{-1} (stretching vibrations), 1580-1640 cm^{-1} (scissoring modes), 1100-1300 cm^{-1} (rocking/twisting modes) and 585-710 cm^{-1} (wagging modes) [62]. For the title compound, the NH_2 modes are assigned at, 3550, 3470 cm^{-1} (IR), 3575, 3450 cm^{-1} (DFT) (stretching modes); 1540, 1245 cm^{-1} (IR), 1244, 582 cm^{-1} (Raman), 1540, 1248, 588 cm^{-1} (DFT) (deformation modes). The NH_2 stretching modes more are pure with 100% PED and high IR intensity and Raman activities. For all the NH_2 deformation modes the Raman activities are low and for the mode at 1540 cm^{-1} the IR intensity is high. According to literature the C-N stretching modes are expected in the range 1400-1000 cm^{-1} [67, 68] and for the title compound these modes observed at 1391, 1133 cm^{-1} in the IR spectrum, 1390, 1211, 1133 cm^{-1} in the Raman spectrum and at 1392, 1315, 1219, 1132 cm^{-1} theoretically with PEDS 36-45%. For these CN stretching modes the IR intensity is high but all the modes possess a low Raman activity.

For the CH_2 groups, the stretching, scissoring, wagging, twisting and rocking modes appear in the ranges 3050-2935 cm^{-1} , 1500-1400 cm^{-1} , 1400-1250, 1200-1100 and 1100-800 cm^{-1} [62, 67]. The CH_2 modes of the title compound are assigned at 3007, 2990, 2880, 2871 cm^{-1} (IR), 3008, 2980, 2945, 2888 cm^{-1} (Raman), 3011-2872 cm^{-1} (DFT) (stretching) and 1447, 1412, 1391, 1345, 1313, 1257, 1203, 1075 cm^{-1} (IR), 1418, 1390, 1348, 1303, 1257, 1070, 1039, 1003 cm^{-1} (Raman), 1444-999 cm^{-1} (DFT) (deformation modes).

For mono-substituted phenyl ring, the CH stretching modes are expected above 3000 cm^{-1} [62] and DFT calculations give these modes in the range 3067-3034 cm^{-1} and experimentally bands are observed at 3070, 3056, 3031 cm^{-1} in the IR spectrum and at 3070, 3052, 3040 cm^{-1} in

the Raman spectrum. The phenyl ring stretching modes are assigned at 1558, 1467 cm^{-1} in the IR spectrum, 1590, 1563, 1465 cm^{-1} in the Raman spectrum and at 1580, 1561, 1467, 1428, 1295 cm^{-1} theoretically as expected [62]. The ring breathing mode of the mono-substituted phenyl ring appears as a weak band near 1000 cm^{-1} [64, 69] and for the title compound the band at 977 cm^{-1} theoretically is assigned as this mode and no band is seen in the IR spectrum as expected. For the ring breathing mode the IR intensity is low, 1.34 with a PED contribution of 56%. The in-plane and out-of-plane CH deformation modes are expected above and below 1000 cm^{-1} [62] and in the present case these modes are assigned at 1288, 1175, 1155, 1012 cm^{-1} (IR), 1287, 1174, 1157, 1020 cm^{-1} (Raman), 1285, 1175, 1158, 1064, 1010 cm^{-1} (DFT) (in-plane deformations) and at 955, 906, 698 cm^{-1} (IR), 953, 905, 695 cm^{-1} (Raman), 968, 953, 904, 831, 691 cm^{-1} (DFT) (out-of-plane deformations).

3.4 UV-Visible spectral analysis

The TD-DFT method is a reliable approach largely used for the prediction absorption wavelengths at a relatively small computing time which corresponds to vertical electronic transitions. For this reason, the electronic absorption spectra of the title compound is theoretically calculated by the TD-DFT/B3LYP/6-311++G(d,p) method using the optimized ground state geometries and these are performed in methanol solvent. The electronic absorption spectra of the investigated compound show an electronic absorption band with maxima at 215 nm (Fig.6). In general the occupied orbital have π character while unoccupied ones have π^* character. The transition is mainly due to the transition HOMO-LUMO that is the π - π^* transition predicted. The transitions, wavelength, oscillator strengths, CI coefficient and dominant contribution (%) in methanol can be seen in Table 5.

3.5 Frontier molecular orbital analysis

The molecular orbital and their properties such as energy are useful for predicting most reactive position in π -electron and conjugated systems [70]. The energies of HOMO and LUMO orbital and their energy gap reflect the biological activity of a molecule. High chemical reactivity and low kinetic stability are associated with a molecule having a small frontier HOMO-LUMO energy gap [71, 72]. For the title compound, the energies of HOMO and LUMO orbital are -8.559 and -4.634 eV respectively. The global chemical descriptors associated with a molecule are: ionization potential $I = -E_{\text{HOMO}} = 8.559 \text{ eV}$, electron affinity $A = -E_{\text{LUMO}} = 4.634 \text{ eV}$, electronegativity $\chi = (I+A)/2 = 6.5965$, global hardness $\eta = (I-A)/2 = 1.9625$, chemical potential

$\mu = -(I+A)/2 = -6.5965$ and electrophilicity index, $\omega = \mu^2/2\eta = 11.086\text{eV}$ [73, 74]. The HOMO-LUMO plots is given in Fig.7 and from this plot it is clear that HOMO is localized over the entire molecule except the phenyl ring while the LUMO is localized over the phenyl ring. This shows that there is a charge transfer process in the molecular system.

3.6 Molecular Electrostatic Potential

Molecular electrostatic potential is a useful descriptor for analyzing the sites for nucleophilic and electrophilic reactions [75] and for predicting the reactive sites for nucleophilic and electrophilic attacks, the MEP at the B3LYP/6-311++G(d,p) (5D, 7F) optimized geometry of the title compound was calculated and the MEP plot is given in Fig.8. MEP provides a visual method to understand the relative polarity of the molecule and the potential is represented by different colors; most negative regions are represented by red, most positive regions are represented by blue and zero potential is by green. From the MEP plot it is clear that the carbonyl groups are the most negative regions, electrophilic regions and the nitrogen atoms are the most positive regions, nucleophilic regions.

3.7 ALIE surfaces, Fukui functions and non-covalent interactions

Average local ionization energy (ALIE) was introduced by Sjoberg et al. [76, 77] and is defined as following:

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

where $\rho_i(\vec{r})$ represents the electronic density of the i -th molecular orbital at the point $\vec{r}$, ϵ_i represents the orbital energy and $\rho(\vec{r})$ is the total electronic density function. Beside MEP this quantum molecular descriptor is also frequently used to determine the molecule sites prone to electrophilic attacks. In fact, for these purposes, ALIE is even better than MEP as it represents the molecule areas where electrons are least tightly bound and therefore where they are the most easily removed. In this work we have calculated ALIE and mapped to the electron density surface, Fig.9. It can be seen in Fig.9, according to the spatial distribution of red color, that electrons are most easily removed from the carbon atoms of benzene ring, oxygen atoms O3 and O29 and nitrogen atom N1. Taking into account the definition of ALIE it can be stated that these locations are prone to electrophilic attacks. In Fig. 9, one intra-molecular non-covalent interaction is also displayed and it is located between atoms O29–H21. Its structural influence may refer to the rotation possibilities of bonds between atoms C8–C11 and N7–C8.

Besides ALIE, it is useful to locate molecule sites that gain or lose electron density once the molecule is subjected to the nucleophilic or electrophilic attack. This is done by the Fukui functions, which are also important quantum molecular descriptors of local reactivity properties of molecules. In the finite difference approach Fukui functions are defined as follows:

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

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

where N denotes the number of electrons in the reference state of the molecule and δ represents the fraction of electron, which is set to be 0.01 [78].

Fukui f^+ function is related to the case when certain amount of charge is added to the molecule so purple color in Fig.10 denotes locations where electron density is gained. On the other side Fukui f^- function is related to the case when certain amount of charge is removed from the molecule and the red color denotes locations where electron density is lost. In this way possible reaction centers are determined. Fukui functions, as mapped to the electron density surface, of title molecule are presented in Fig.10. Results of Fukui functions indicate that main reaction centers of title compound are possibly carbon atoms of benzene ring. Namely, in the case of Fukui f^+ function, after addition of charge, electron density increased in the near vicinity of carbon atoms C14, C16 and C20. On the other side, results of Fukui f^- function indicate that electron density decreased in the near vicinity of carbon atom C16, after removal of charge.

3.8 Nonlinear optical properties

Nonlinear optical properties finds applications in telecommunication, second harmonic wave generation, signal processing, optical interconnections, optical phase conjugation and optical mixing [79]. The polarizability, first and second order hyperpolarizabilities of the title compound were calculated using DFT- B3LYP/6-311++G(d,p) (5D, 7F) method to investigate the relationships among molecular structures and nonlinear optical properties. The dipole moment and mean polarizability values of the title compound are 1.1265 Debye and 2.3606×10^{-23} esu. The first order hyperpolarizability of the title compound is calculated and is found to be 1.2274×10^{-30} esu which is 9.44 times that of the standard NLO material urea [80]. The average second hyperpolarizability is -92.35×10^{-37} esu and we conclude that the title compound and its derivatives are good materials for future studies on NLO properties.

3.9 Natural bonding orbital analysis

The natural bond orbital (NBO) calculations were performed using NBO 3.1 program [81] as implemented in the Gaussian09 package at the B3LYP method with the 6-311++G(d,p) (5D, 7F) level which provides a convenient basis for investigation charge transfer or conjugative interactions in molecular system [82]. The second order Fock matrix was carried out to evaluate the donor–acceptor interactions in the NBO analysis [83]. The perturbation energies of significant donor-acceptor interactions are presented in Table 6. The larger the E(2) value, the intensive is the interaction between electron donors and electron acceptors. The strong interaction $n_1N_7 \rightarrow \pi^*(C_{22}-O_{29})$ has the highest E(2) value 65.38 kJ/mol and a very strong interaction has been in $n_1N_1 \rightarrow \pi^*(O_3-C_4)$ with an energy of 55.68 kJ/mol. Table 7 gives the occupancy of electrons and p-character [84] in significant NBO natural atomic hybrid orbital. Almost 100% p-character was observed in π -bonding of O_3-C_4 , $C_{22}-O_{29}$ and the lone pairs of n_1N_1 , n_2O_2 , n_2O_3 , n_1N_7 and n_2O_{29} .

3.10 Reactive properties based on autoxidation and hydrolysis

In this work we have calculated BDE for all single acyclic bonds of the title molecule. From one side BDEs of hydrogen abstraction allow prediction of possible molecule sites that are prone to oxidation. On the other side, BDEs of the rest of the single acyclic bonds allow prediction of the bonds that could be broken first. The crucial moment that determines the rate in autoxidation process is related to the abstraction of hydrogen atom from the parent drug molecule by peroxy radical [85, 86]. All peroxy radicals have similar BDE values which are in the range of 87 kcal/mol to 92 kcal/mol and these values can be considered as independent of the chemical surrounding [85, 87]. Thus, by calculating BDE for hydrogen abstraction and comparing obtained results with the mentioned energy interval, positions of a molecule possibly prone to oxidation can be found. According to the study done by Wright et al. [88] it can be concluded that intermediate range of 70–85 kcal/mol for BDE indicates the highest risk of some molecule to be sensitive toward autoxidation [85, 88], while BDE values below 70–75 kcal/mol are not suitable for the degradation by autoxidation.

Results concerning the BDEs of all single acyclic bonds have been presented in Fig.11. BDE for hydrogen abstraction are given in red color, while BDE for the rest of the single acyclic bonds are given in blue color. As it can be seen in provided results one BDE for hydrogen abstraction has value of below 92 kcal/mol and that bond is the one denoted with number 7, so it

could be expected that degradation via autoxidation process is possible but it is not very likely because this value is still significantly higher than 85 kcal/mol. On the other side, the lowest BDEs have been calculated for bonds denoted with 10 and 11 indicating that degradation could start here, as the lowest amounts of energy are needed for their breaking.

To investigate possible interactions of title molecule's atoms with water molecules we have calculated RDF after MD simulations. RDF, $g(r)$, denotes probability of finding a particle in the distance r from another particle [89] and in cases of molecular dynamics this important quantity indicates, according to the curve profile and peak distance, to what extent are significant interactions with solvent (in this case water) molecules. Significant RDFs are presented in Fig.12. RDFs indicate that four carbon, three hydrogen, one nitrogen and one oxygen atoms have significant interactions with water molecules. RDF curves of carbon atoms C4, C14, C18 and C23 are of very similar shape and peak distance. In these cases maximal $g(r)$ values are in the range from 1.1 to 1.3, while peak distance is around 3.5Å. On the other side, RDFs of non-carbon atoms are indicating much more significant interactions with water molecules, especially in the cases of hydrogen atoms H30 and H31 with peak distance value of below 2Å and $g(r)$ values of 1.15 and 0.85, respectively. Hydrogen atoms H31 and H6 have two distinct solvation spheres, with peak distances at around 3.25Å and 5.25Å. Nitrogen atom N1 and oxygen atom O3 are having almost same peak distance and $g(r)$ values, with $g(r)$ curve being much sharper for oxygen atom, indicating stronger interactions with water. The fact that the most significant interactions are having atoms N1, O3, C4, H30 and H31 is very important because the bond with the lowest value of BDE, bond 10, is located very close to them. This indicates that the role of hydrolysis mechanism in degradation of the title compound could be very significant.

3.11 Mulliken atomic charges

The atomic charge in molecules is fundamental to chemistry. The charge distribution on the molecule has an important role in the application of quantum mechanical calculations for the molecular system. Atomic charge affects dipole moment, polarizability, electronic structure and other molecular properties of the system. Mulliken charges are calculated by determining the electron population of each atom as defined in the basic functions. The charge distributions calculated by the Mulliken [90]. The Mulliken atomic charges of title molecule calculated by DFT method at 6-311++G(d,p) basic set in gaseous phase are given in Table 8. It is worthy to mention that C22 (0.170e), C4 (0.186e) atoms exhibit positive charges, it is due to substitution of

electronegative atoms like oxygen and nitrogen, become more acidic, while others carbon atoms exhibit negative charge. Oxygen and nitrogen has a maximum negative charge value of about O3(-0.297e), O29(-0.287e) and N1(-0.438e) at same level basic set. However all the hydrogen atoms exhibit net positive charge and the magnitudes are changing between 0.148e and 0.256e and but H atoms accommodate more positive atomic charges H30 and H31 0.266e and 0.399e, respectively, than the other hydrogen atoms and is acidic. The presence of large negative charge on oxygen and nitrogen atom O3 (-0.297 e), O29 (-0.287e) and N1 (-0.438) and a net positive charge on hydrogen atom (H30 and H31 0.266 e and 0.399e, respectively) may suggest the formation of N1-H31...O3 and N1-H30...O29 intermolecular hydrogen bonding.

3.12 Temperature dependence of 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. Information of permanent dipole moment of a molecule permits us to determine molecule's confirmation. The thermodynamic parameter 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 S1 (supporting information) such as dipole moment, thermal energy and zero point vibrational energy. Scale factors have been recommended [91] 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 (DH) in the temperature range 100–1000 K and presented in Table S2 (supporting information) and Figs.S1-S3 (supporting material) and 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 [92].

3.13 Molecular docking

Morpholine is an organic compound which is considered as an important building block in the field of medicinal chemistry. The pyrrole derivatives are anticancer agents [93] including hedgehog-dependent cancer [94]. Thus we choose pyrrole inhibitor as a target for docking simulation. High resolution crystal structure of pyrrole inhibitor was downloaded from the RCSB protein data bank website with PDB ID: 4A4L and the molecular docking calculations were performed on Auto Dock-Vina software [95] and as reported in literature [96]. The docking protocol predicted the same conformation as was present in the crystal structure with RMSD

value well within the reliable range of 2 Å [97]. Amongst the docked conformations, one which binds well at the active site was analyzed for detailed interactions in Discovery Studio Visualizer 4.0 software. The ligand binds at the active site of the substrate by weak non-covalent interactions with ten conformations as shown in Fig.13. Amino acid Glu131, Cys133, Cys67 forms H-bond with NH₂ group, oxygen atom, phenyl ring respectively. Phe188 shows π - π T-shaped hydrophobic interaction with phenyl ring. The docked ligand, title compound forms a stable complex with pyrrole inhibitor (Fig.14) and gives a binding affinity (ΔG in kcal/mol) value of -7.5 (Table 9). These results suggest that the compound might exhibit inhibitory activity against pyrrole inhibitor.

3.14 Antimicrobial activity

Synthesized compound have been screened in-vitro for their antibacterial activity against gram negative bacteria *Pseudomonas aureginosa* (MTCC-1035), *Escherichia Coli* (MTCC-1687) and gram positive bacteria *Becillus Cereus* (MTCC-430), *Bacillus Subtilis* (MTCC-441) by disc diffusion method using DMSO as solvent [98]. Inhibition zones (IZ) in mm of the test compounds were measured after 24-48 h incubation at 37°C for bacteria. Standard antibacterial Tetracycline was used under similar condition for comparison. Control test with solvents was performed for every assay but showed no inhibition of microbial growth. The results show (Table.10) that the synthesized compound was moderate to good activity against the tested microorganisms. They displayed good antibacterial activity against gram-positive (*Escheria Coli*) and gram-negative bacterial strains (*Bacillus Subtilis*).

4. Conclusion

The vibrational spectral analysis and single crystal XRD structure of 4-benzyl-5-oxomorpholine-3-carbamide were carried out for exploring the chemical and pharmacological properties. The crystal structure of the compound features two strong hydrogen bonds involving the amide group. From the single crystal XRD structure and optimized geometry, it is clear that the two rings in the title molecule are tilted from each other. The ring breathing mode of the phenyl ring is assigned at 977 cm⁻¹ theoretically with a PED contribution of 56%. HOMO is localized over the entire molecule except the phenyl ring while the LUMO is localized over the phenyl ring which gives transfer process in the molecular system. From the MEP plot analysis, it is clear that carbonyl groups are electrophilic regions and nitrogen atoms are the nucleophilic regions. First order hyperpolarizability is 9.44 times that of the standard NLO material urea.

ALIE surfaces recognize, beside carbon atoms of benzene ring, nitrogen atom N1 and oxygen atoms O3 and O29 as possible reaction centers, from the aspect of electrophilic attacks. Benzene ring is also important from the aspect of local reactivity, according to the results obtained by Fukui functions as well. Only one intra-molecular non-covalent interaction has been detected, located between atoms O29 and H21. BDE for abstraction of hydrogen atom H25 is having value of ~90.5 kcal/mol, so it could be expected that degradation via autoxidation process is possible. Bonds 10 and 11 are having the lowest BDE values, ~74 kcal/mol and ~77 kcal/mol, respectively. This information is very important because all atoms (with single acyclic bonds) in close vicinity of bond 10 are having significant interactions with water molecules, indicating that degradation process could be under significant influence of hydrolysis mechanism. Docking studies reveal that amino acid Glu131, Cys133, Cys67 forms H-bond with NH₂ group, oxygen atom, phenyl ring respectively and Phe188 shows π - π T-shaped hydrophobic interaction with phenyl ring. The title compound shows good antibacterial activity against gram-positive and gram-negative bacterial strains.

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Supplementary Material

The cif file of the title compound have been assigned CCDC number 1443690 and can be obtained free of cost on application to CCDC 12 Union Road, Cambridge CB21 EZ, UK. (Fax: (+44) 1223 336-033; e-mail: data_request@ccdc.cam.ac.uk).

References

- [1] R. Wijtmans, M.K.S. Vink, H.E. Schoemaker, F.L. van Delft, R.H. Blaauw, F.P.J.T. Rutjes, Bioloical relevance and synthesis of C-substituted morpholine derivatives, *Synthesis* 5 (2004) 641-662.

- [2] T.X. Meitro, A. Cochi, D.G. Pardo, J. Cossy, Asymmetric synthesis of an antagonist of neurokinin receptor, SSR 241586, *J. Org. Chem.* 76 (2011)2594-2602.
- [3] R.J. Lukas, A.Z. Muresan, M.I. Damaj, B.E. Blough, X. Huang, H.A. Navarro, S.W. Mascarella, J.B. Eaton, S.K. Marxer-Miller, F.I. Carroll, Synthesis and characterization of in vitro and in vivo profiles of hydroxybutyropion analogues, aids to smoking cessation, *J. Med. Chem.* 53 (2010) 4731-4748.
- [4] X. Sun, L. Niu, X. Li, X. Lu, F. Li, Characterization of metabolic profile of mosapride citrate in rat and identification of two new metabolites, mosapride N-oxide and morpholine ring opened mosapride by UPLC-ESI-MS/MS, *J. Pharm. Biomed. Anal.* 50 (2009) 27-34.
- [5] F. Micheli, S. Cremonesi, T. Semeraro, L. Tarsi, S. Tomelleri, P. Cavanni, B. Oliosi, E. Perdoni, A. Sava, L. Zonzini, A. Feriani, S. Braggio, C. Heidbreder, Novel morpholine scaffolds as selective dopamine (DA) D3 receptor antagonists, *Bioorg. Med. Chem. Lett.* 26 (2016) 1329-1332.
- [6] P. Ghosh, M.J. Deka, A.K. Saikia, Lewis acid mediated intramolecular C-O bond formation of alkanol-epoxide leading to substituted morpholine and 1,4-oxazepane derivatives, total synthesis of viloxazine, *Tetrahedron* 72 (2016) 690-698.
- [7] H. Hamidian, S. Azizi, Synthesis of novel compounds containing morpholine and 5(4H)-oxazolone rings as potent tyrosinase inhibitors, *Bioorg. Med. Chem.* 23 (2015) 7089-7094.
- [8] E.M. Ladopoulou, A.N. Matralis, A. Nikitakis, A.P. Kourounakis, Antihyperlipidemic morpholine derivatives with antioxidant activity: An investigation of the aromatic substitution, *Bioorg. Med. Chem.* 23 (2015) 7015-7023.
- [9] H. Takahata, S. Takahashi, S.I. Kouno, T. Momose, Symmetry assisted synthesis of C2-symmetric trans- α,α' -bis(hydroxymethyl)pyrrolidine and piperidine derivatives via double Sharpless asymmetric dihydroxylation of α,ω -terminal dienes, *J. Org. Chem.* 63 (1998) 2224-2231.
- [10] J.M. Betancort, C.F. Barbas, Catalytic direct asymmetric Michael reactions, taming naked aldehyde donors, *Org. Lett.* 3 (2001)3737-3740.

- [11] R. Dave, N.A. Sasaki, Facile route to 3,5-disubstituted morpholines, enantioselective synthesis of O-protected trans-3,5-bis(hydroxymethyl)morpholines, *Org. Lett.* 6 (2003) 15-18.
- [12] S. Mayer, B. List, Asymmetric counter anion directed catalysis, *Angew. Chem. Int. Ed.* 45 (2006) 4193-4195.
- [13] Y.C. Quin, L. Pu, Highly enantioselective addition of diphenylzinc to aliphatic and aromatic aldehydes catalyzed by a readily available H8-binol derivatives, *Angew. Chem. Int. Ed.* 45 (2006) 273-277.
- [14] S.G. Nelson, K. Wang, Asymmetric claisen rearrangements enabled by catalytic asymmetric di(allyl) ether synthesis, *J. Am. Chem. Soc.* 128 (2006) 4232-4233.
- [15] S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, 3,3'-bimorpholine derivatives as a new class of organocatalysts for asymmetric Michael addition, *Org. Lett.* 8 (2006) 2559-2562.
- [16] N.J. Leonard, K. Jann, A new synthesis of aziridinium salts, 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate, a prototype, *J. Am. Chem. Soc.* 82 (1960) 6418-6419.
- [17] N.J. Leonard, K. Jann, Small charges ring, II, the synthesis of aziridinium salts, *J. Am. Chem. Soc.* 84 (1962) 4806-4813.
- [18] Y. Kogami, K. Okawa, Synthesis of optically active 3-morphinecarboxylic acid and tetrahydro-2H-1,4-thiazine-3-carboxylic acid, *Bull. Chem. Soc. Jpn.* 60 (1987) 2963-2965.
- [19] R. Pedrosa, C. Andres, P. Mendiguchia, J. Nieto, Diastereoselective synthesis of enantiopure morpholines by electrophilic selenium induced 6-exo cyclizations on chiral 3-alkyl-2-hydroxymethylperhydro-1,3-benzoxazine derivatives, *J. Org. Chem.* 71 (2006) 8854-8863.
- [20] F. Sladojevich, A. Trabocchi, A. Guarna, Convenient route to enantiopure fmoc protected morpholine-3-carboxylic acid, *J. Org. Chem.* 72 (2007) 4254-4257.
- [21] T.X. Metro, D.G. Pardo, J. Cossy, Syntheses of (S,S)-reboxetine via a catalytic stereo specific rearrangement of β -amino alcohols, *J. Org. Chem.* 73 (2008) 707-710.

- [22] M. Yar, E.M. McGarrigle, V. K. Aggarwal, Novel annulation reaction for the synthesis of morpholines, thiomorpholines and piperazines from β -heteroatom compounds and vinyl sulfonium salts, *Angew. Chem., Int. Ed.* 47 (2008) 3784-3786.
- [23] M.K. Ghorai, D. Shukla, K. Das, Enantioselective syntheses of morpholines and their homologues via SN2-type ring opening of aziridines and azetidines with haloalcohols, *J. Org. Chem.* 74 (2009) 7013-7022.
- [24] L. Wang, Q.B. Liu, D.S. Wang, X. Li, X.W. Han, W.J. Xiao, Y.G. Zhou, Tandem ring opening/closing reactions of N-Ts aziridines and aryl propargyl alcohols promoted by t-BuOK, *Org. Lett.* 11 (2009) 1119-1122.
- [25] R.T. Sawant, J. Stevenson, L.R. Odell, P.I. Arvidsson, Organocatalytic asymmetric cross aldol reaction of 2-chloroethoxy acetaldehyde, diversity oriented synthesis of chiral substituted 1,4-dioxanes and morpholines, *Tetrahedron: Asymmetry*, 24 (2013) 134-141.
- [26] A. Golubovic, B. Abramovic, M. Scepanovic, M. Grujic-Brojcin, S. Armakovic, I. Veljkovic, B. Babic, Z. Dohcevic-Mitrovic, Z. Popovic, Improved efficiency of sol-gel synthesized mesoporous anatase nanopowders in photocatalytic degradation of metoprolol, *Mater. Res. Bull.* 48 (2013) 1363-1371.
- [27] R. Ma, B. Wang, S. Lu, Y. Zhang, L. Yin, J. Huang, S. Deng, Y. Wang, G. Yu, Characterization of pharmaceutically active compounds in Dongiting Lake, China: Occurrence, chiral profiling and environmental risk, *Sci. Total Environ.* 557 (2016) 268-275.
- [28] S.J. Armaković, S. Armaković, N.L. Finčur, F. Šibul, D. Vione, J.P. Šetrajčić, B. Abramović, Influence of electron acceptors on the kinetics of metoprolol photocatalytic degradation in TiO₂ suspension: A combined experimental and theoretical study, *RSC Advances* 5 (2015) 54589-54604.
- [29] B. Abramovic, S. Kler, D. Sojic, M. Lausevic, T. Radovic, D. Vione, Photocatalytic degradation of metoprolol tartrate in suspensions of two TiO₂-based photocatalysts with different surface area. Identification of intermediates and proposal of degradation pathways, *J. Hazard. Mater.* 198 (2011) 123-132.
- [30] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, OLEX2, a complete structure solution, refinement and analysis program, *J. Appl. Cryst.* 42 (2009) 339-341.

- [31] L.J. Bourhis, O.V. Dolomanov, R.J. Gildea, J.A.K. Howard, H. Puschmann, The anatomy of a comprehensive constrained, restrained refinement program for the modern computing environment, *Olex2 dissected*, *Acta Cryst.* A71 (2015) 59-75.
- [32] G.M. Sheldrick, A short history of SHELX, *Acta Cryst.* A64 (2008) 112-122.
- [33] Gaussian 09, Revision B.01, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian, Inc., Wallingford CT, 2010.
- [34] R. Dennington, T. Keith, J. Millam, Gaussview, version 5, Semichem Inc., ShawneeMission, KS, 2009.
- [35] J.B. Foresman, Pittsburg, PA, in: E. Frisch (Ed.), *Exploring Chemistry with Electronic Structure Methods: a Guide to Using Gaussian*, 1996.
- [36] J.M.L. Martin, C. Van Alsenoy, GAR2PED, A Program to Obtain a Potential Energy Distribution from a Gaussian Archive Record, University of Antwerp, Belgium, 2007.
- [37] A.D. Bochevarov, E. Harder, T.F. Hughes, J.R. Greenwood, D.A. Braden, D.M. Philipp, D. Rinaldo, M.D. Halls, J. Zhang, R.A. Friesner, Jaguar: A High performance Quantum Chemistry Software Program with Strengths in Life and Materials Sciences, *Int. J. Quantum Chem.* 113 (2013) 2110-2142.
- [38] Materials Science Suite 2015-4, Schrodinger, LLC, New York, NY, 2015.
- [39] A. Otero-de-la-Roza, E.R. Johnson, J. Contreras-García, Revealing non-covalent interactions in solids: NCI plots revisited, *Phys. Chem. Chem. Phys.* 14 (2012) 12165-12172.

- [40] E.R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A.J. Cohen, W. Yang, Revealing noncovalent interactions, *J. Am. Chem. Soc.* 132 (2010) 6498-6506.
- [41] D. Shivakumar, J. Williams, Y. Wu, W. Damm, J. Shelley, W. Sherman, Prediction of absolute solvation free energies using molecular dynamics free energy perturbation and the OPLS force field, *J. Chem. Theory Comput.* 6 (2010) 1509-1519.
- [42] Z. Guo, U. Mohanty, J. Noehre, T.K. Sawyer, W. Sherman, G. Krilov, Probing the α -helical structural stability of stapled p53 peptides: Molecular dynamics simulations and analysis, *Chem. Biol. Drug Design* 75 (2010) 348-359.
- [43] K.J. Bowers, E. Chow, H. Xu, R.O. Dror, M.P. Eastwood, B.A. Gregersen, J.L. Klepeis, I. Kolossvary, M.A. Moraes, F.D. Sacerdoti, *Scalable algorithms for molecular dynamics simulations on commodity clusters*. in *SC 2006 Conference, Proceedings of the ACM/IEEE*. 2006. IEEE.
- [44] *Schrödinger Release 2015-4: Desmond Molecular Dynamics System, version 4.4*, D. E. Shaw Research, New York, NY, 2015. *Maestro-Desmond Interoperability Tools, version 4.4*, Schrödinger, New York, NY, 2015. 2015.
- [45] J.L. Banks, H.S. Beard, Y. Cao, A.E. Cho, W. Damm, R. Farid, A.K. Felts, T.A. Halgren, D.T. Mainz, J.R. Maple, R. Murphy, D.M. Philipp, M.P. Repasky, L.Y. Zhang, B.J. Berne, R.A. Friesner, E. Gallicchio, R.M. Lew, Integrated modeling program, applied chemical theory (IMPACT), *J. Comput. Chem.* 26 (2005) 1752-1780.
- [46] H.J. Berendsen, J.P. Postma, W.F. van Gunsteren, J. Hermans, *Interaction models for water in relation to protein hydration*, in *Intermolecular forces*. 1981, Springer. p. 331-342.
- [47] M.A. Spackman, P.G. Byrom, A novel definition of a molecule in a crystal, *Chem. Phys. Lett.* 267 (1997) 215-220.
- [48] J.J. McKinnon, A.S. Mitchell, M.A. Spackman, Hirshfeld surfaces, a new tool for visualising and exploring molecular crystals, *Chem. Eur. J.* 4 (1998) 2136-2141.
- [49] M.A. Spackman, D. Jayatilaka, Hirshfeld surface analysis, *Cryst. Eng. Comm.* 11 (2009) 19-32.
- [50] H.F. Clausen, M.S. Chevallier, M.A. Spackman, B.B. Iversen, Three new co-crystals of hydroquinone, crystal structures and Hirshfeld surface analysis of intermolecular interactions, *New J. Chem.* 34 (2010) 193-199.

- [51] A.L. Rohl, M. Moret, W. Kaminsky, K. Claborn, J.J. McKinnon, B. Kahr, Hirshfeld surfaces identify inadequacies in computations of intermolecular interactions in crystals, pnetamorphic 1,8-dihydroxyanthraquinone, *Cryst. Growth Des.* 8 (2008) 4517-4525.
- [52] A. Parkin, G. Barr, W. Dong, C.J. Gilmore, D. Jayatilaka, J.J. McKinnon, M.A. Spackman, C. C. Wilson, Comparing entire crystal structures, structural genetic fingerprinting, *Cryst. Eng. Comm.* 9 (2007) 648-652.
- [53] M.A. Spackman, J.J. McKinnon, Fingerprinting intermolecular interactions in molecular crystals, *Cryst. Eng. Comm.* 4 (2002) 378-392.
- [54] P.A. Wood, J.J. McKinnon, S. Parsons, E. Pidcock, M.A. Spackman, Analysis of the compression of molecular crystal structures using Hirshfeld surfaces, *Cryst. Eng. Comm.* 10 (2008) 368-376.
- [55] S.K. Wolff, D.J. Grimwood, J.J. McKinnon, D. Jayatilaka, M.A. Spackman, *Crystal Explorer 2.0*; University of Western Australia: Perth, Australia, 2007; <http://hirshfeldsurfacenet.blogspot.com/>.
- [56] C.F. Macrae, I.J. Bruno, J.A. Chisholm, P.R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P.A. Wood, Mercury CSD 2.0, new features for the visualization and investigation of crystal structures, *J. Appl. Cryst.* 41(2008) 466-470.
- [57] K. Tamagawa, T. Iijima, M. Kimura, Molecular structure of benzene, *J. Mol. Struct.* 30 (1976) 243-253.
- [58] J. Lukose, C.Y. Panicker, P.S. Nayak, B. Narayana, B.K. Sarojini, C. Van Alsenoy, A.A. Al-Saadi, Synthesis, structural and vibration investigation of 2-phenyl-N-(pyrazin-2-yl)acetamide combining XRD diffraction, FT-IR and NMR spectroscopies with DFT calculations, *Spectrochim. Acta* 135 (2015) 608-616.
- [59] S.M. Bakalova, A.G. Santos, I. Timcheva, J. Kaneti, I.L. Filipova, G.M. Dobrikov, V.D. Dimitrov, Electronic absorption and emission spectra and computational studies of some 2-aryl, 2-styry and 2-(4'-aryl)butadienyl quinazolin-4-ones, *J. Mol. Struct. Theochem.* 710 (2004) 229-234.
- [60] S.H.R. Sebastian, A.M.S. Al-Tamimi, N.R. El-Brollosy, A.A. El-Emam, C.Y. Panicker, C. Van Alsenoy Vibrational spectroscopic (FT-IR and FT-Raman) studies, HOMO-LUMO, NBO analysis and MEP of 6-methyl-1-((E)-2-methyl-3-phenyl-prop-2-en-1-

- yl]oxy}methyl)-1,2,3,4-tetra-hydroquinazoline-2,4-dione, a potential chemotherapeutic agent, using density functional method, *Spectrochim. Acta* 134 (2015) 316-325.
- [61] G. Socrates, *Infrared Characteristic Group Frequencies*, John Wiley and Sons, New York, 1981.
- [62] N.P.G. Roeges, *A Guide to the Complete Interpretation of Infrared Spectra of Organic Structures*, Wiley, New York, USA, 1994.
- [63] A.S. El-Azab, Y.S. Mary, C.Y. Panicker, A.A.M. Abdel-Aziz, M.A. El-Sherbeny, C. Van Alsenoy, DFT and experimental (FT-IR and FT-Raman) investigation of vibrational spectroscopy and molecular docking study of 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-(3,4,5-trimethoxyphenyl) acetamide, *J. Mol. Struct.* 1113 (2016) 133-145.
- [64] B. Smith, *Infrared Spectral Interpretation, A Systematic Approach*, CRC Press, Washington DC, 1999.
- [65] Y.S. Mary, K. Raju, C.Y. Panicker, A.A. Al-Saadi, T. Thiemann, Molecular conformational analysis, vibrational spectra, NBO analysis and first hyperpolarizability of (2E)-3-(3-chlorophenyl)prop-2-enoic anhydride based on density functional theory calculations, *Spectrochim. Acta* 131 (2014) 471-483.
- [66] Y.S. Mary, K. Raju, C.Y. Panicker, A.A. Al-Saadi, T. Thiemann, C. Van Alsenoy, Molecular conformational analysis, vibrational spectra, NBO analysis and first hyperpolarizability of (2E)-3-phenylprop-2-enoic anhydride based on density functional theory calculations, *Spectrochim. Acta* 128 (2014) 638-646.
- [67] N.B. Colthup, L.H. Daly, S.E. Wiberly, *Introduction to Infrared and Raman Spectroscopy*, ed.3, Academic Press, Boston, USA, 1990.
- [68] R.M. Silverstein, G.C. Bassler, T.C. Morrill, *Spectrometric Identification of Organic Compounds*, fifth ed., John Wiley and Sons Inc., Singapore, 1991.
- [69] G. Varsanyi, *Assignments of Vibrational Spectra of Seven Hundred Benzene Derivatives*, Wiley, New York, 1974.
- [70] K. Fukui, T. Yonezawa, H. Shingu, A molecular orbital theory of reactivity in aromatic hydrocarbons, *J. Chem. Phys.* 20 (1952) 722-726.
- [71] N. Choudhary, S. Bee, A. Gupta, P. Tandon, Comparative vibrational spectroscopic studies, HOMO-LUMO and NBO analysis of N-(phenyl)-2,2-dichloroacetamide, N-(2-

- chlorophenyl)-2,2-dichloroacetamide and N-(4-chlorophenyl)-2,2-dichloroacetamide based on density functional theory, *Comp. Theor. Chem.* 1016 (2013) 8-21.
- [72] B. Kosar, C. Albayrak, Spectroscopic investigations and quantum chemical computational study of (E)-4-methoxy-2-[(p-toylimino)methyl]phenol, *Spectrochim. Acta* 78 (2011) 160-167.
- [73] T.A. Koopmans, Über die zuordnung von wellenfunktionen und eigenwerten zu den einzelnen elektronen eines atoms, *Physica* 1 (1993) 104-113.
- [74] R.J. Parr, L.V. Szentpaly, S. Liu, Electrophilicity index, *J. Am. Chem. Soc.* 121 (1999) 1922-1924.
- [75] V. Karunakaran, V. Balachandran, FT-IR, FT-Raman spectra, NBO, HOMO-LUMO and thermodynamic functions of 4-chloro-3-nitrobenzaldehyde based on ab initio HF and DFT calculations, *Spectrochim. Acta* 98 (2012) 229-239.
- [76] P. Sjöberg, J.S. Murray, T. Brinck, P. Politzer, Average local ionization energies on the molecular surfaces of aromatic systems as guides to chemical reactivity, *Canadian J. Chem.* 68 (1990) 1440-1443.
- [77] P. Politzer, F. Abu-Awwad, J.S. Murray, Comparison of density functional and Hartree-Fock average local ionization energies on molecular surfaces, *Int. J. Quantum Chem.* 69 (1998) 607-613.
- [78] A. Michalak, F. De Proft, P. Geerlings, R. Nalewajski, Fukui functions from the relaxed Kohn-Sham orbitals, *J. Phys. Chem. A* 103 (1999) 762-771.
- [79] V.M. Geskin, C. Lambert, J.L. Bredas, Origin of high second and third order nonlinear optical response in ammonio/borate diphenylpolyene zwitterions, the remarkable role of polarized aromatic groups, *J. Am. Chem. Soc.* 125 (2003) 15651-15658.
- [80] C. Adant, M. Dupuis, J.L. Bredas, Ab initio study of the nonlinear optical properties of urea : Electron correlation and dispersion effects, *Int. J. Quantum. Chem.* 56 (1995) 497-507.
- [81] E.D. Glendening, A.E. Reed, J.E. Carpenter, F. Weinhold, NBO Version 3.1, Gaussian Inc., Pittsburgh, PA, 2003.
- [82] F. Weinhold, C.R. Landis, Introduction to natural bond orbitals, NBO 5.0 program and recent extensions of localized bonding concepts, *Chem. Ed: Res & Pract (CERP; special "structural concepts" issue)*, 2 (2001) 91-104.

- [83] M. Szafram, A. Komasa, E.B.Adamska, Crystal and molecular structure of 4-carboxypiperidinium chloride (4-piperidinecarboxylic acid hydrochloride, J. Mol. Struct. 827 (2007) 101-107.
- [84] A.E. Reed, L.A. Curtiss, F. Weinhold, Intermolecular interactions from a natural bond orbital, donor acceptor view point, Chem. Rev. 88 (1988) 899-926.
- [85] T. Andersson, A. Broo, E. Evertsson, Prediction of drug candidates sensitivity toward autoxidation: computational estimation of C-H dissociation energies of carbon centered radicals, J. Pharm. Sci. 103 (2014) 1949-1955.
- [86] P. Lienard, J. Gavartin, G. Boccardi, M. Meunier, Predicting drug substances autoxidation, Pharm. Res. 32 (2015) 300-310.
- [87] Y.-R.Luo, *Handbook of bond dissociation energies in organic compounds*. 2002: CRC press.
- [88] J.S. Wright, H. Shadnia, L.L. Chepelev, Stability of carbon centered radicals, effect of functional groups on the energetic of addition of molecular oxygen, J. Comput. Chem. 30 (2009) 1016-1026.
- [89] R.V. Vaz, J.R. Gomes, C.M. Silva, Molecular dynamics simulation of diffusion coefficients and structural properties of ketones in supercritical CO₂ at infinite dilution, J. Supercritic. Fluids 107 (2016) 630-638.
- [90] R.S. Mulliken, Electronic population analysis on LCAO-MO molecular wave functions, J. Chem. Phys. 23 (1955) 1833-1840.
- [91] M. A. Palafox, Scaling factors for the prediction of vibrational spectra, I. Benzene molecule, Int. J. Quantum Chem. 77 (2000) 661-684.
- [92] J.B. Ott, J. Boerio-Goates, Chemical Thermodynamics: Advanced Applications, Calculations from Statistical Thermodynamics, Academic Press, 2000.
- [93] F. Bellina, R. Rossi, Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions, Tetrahedron 62 (2006) 7213-7256.
- [94] G.L. Regina, R. Bai, A. Coluccia, V. Famiglini, S. Pelliccia, S. Passacantilli, C. Mazzocchi, V. Ruggieri, L. Sisinni, A. Bolognesi, W.M. Rensen, A. Miele, M. Nalli, R. Alfonsi, L.D. Marcotullio, A. Gulino, A. Brancale, E. Novellino, G. Dondio, S. Vultaggio, M. Varasi, C. Mercurio, E. Hamel, P. Lavia, R. Silvestri, New pyrrole

- derivatives with potent tubulin polymerization inhibiting activity as anticancer agents including hedgehog dependent cancer, *J. Med. Chem.*, 57 (2014) 6531-6552.
- [95] O. Trott, A. J. Olson, AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, *J. Comput. Chem.* 31 (2010) 455-461.
- [96] A.S. El-Azab, K. Jalaja, A.A.-M. Abdel-Aziz, A.M. Al-Obaid, Y.S. Mary, C.Y. Panicker, C. Van Alsenoy, Spectroscopic analysis (FT-IR, FT-Raman and NMR) and molecular docking study of ethyl 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-acetate, *J. Mol. Struct.* 1119 (2016) 451-461.
- [97] B. Kramer, M. Rarey, T. Lengauer, Evaluation of the FlexX incremental construction algorithm for protein ligand docking, *PROTEINS: Struct. Funct. Genet.* 37 (1999) 228-241.
- [98] A.L. Barry, Antimicrobial susceptibility test, Principles and Practices, Lea and Febiger, Philadelphia, 1987.

Figure captions

- Fig.1 FT-IR spectrum of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.2 FT-Raman spectrum of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.3 Hirshfeld surfaces of title compound
- Fig.4 ORTEP view of 4-benzyl-5-oxomorpholine-3-carbamide with thermal ellipsoids drawn at 50 % probability with optimized geometry
- Fig.5. (a) Realization of $C_2^2(11)$ chains along [010] from alternating $R_2^2(8)$ and $R_2^2(14)$ dimeric motifs (b) 1D $C_1^1(5)$ chains observed in the crystal structure when viewed down the a axis (c) Overall two dimensional architecture displayed by the title compound
- Fig.6 UV-Vis spectrum (DFT) of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.7 HOMO-LUMO plots of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.8 MEP plot of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.9. Representative ALIE surface of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.10. Fukui functions of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.11. BDE of all single acyclic bonds of 4-benzyl-5-oxomorpholine-3-carbamide
- Fig.12. RDFs of a) carbon and b) non-carbon atoms with significant interactions with water

Fig.13 Pictorial representation with docked ligand embedded in the active site of pyrrole inhibitor with ten conformations

Fig.14 Schematic for the ligand interaction with H-bond surface of pyrrole inhibitor

Table 1Crystallographic data and refinement parameters of the title compound

Bond precision:	C-C = 0.0025 Å		Wavelength=0.71073
Cell:	<i>a</i> =9.912(5)	<i>b</i> =10.371(5)	<i>c</i> =11.632(6)
	<i>alpha</i> =90	<i>beta</i> =102.36(3)	<i>gamma</i> =90
Temperature: 298 K			
Volume	1168.0(10)		
Space group	<i>P</i> 2 ₁ / <i>n</i>		
Hall group	- <i>P</i> 2 ₁ <i>yn</i>		
Moiety formula	C ₁₂ H ₁₄ N ₂ O ₃		
Sum formula	C ₁₂ H ₁₄ N ₂ O ₃		
Mr	234.25		
D _x ,g cm ⁻³	1.332		
Z	4		
Mu (mm ⁻¹)	0.097		
F ₀₀₀	496.0		
F ₀₀₀ '	496.24		
h,k,l _{max}	11,12,13		
N _{ref}	2062		
T _{min} ,T _{max}	0.976,0.979		
T _{min} '	0.976		
Data completeness=	0.979	Theta(max)= 25.000	
R(reflections)=	0.0391(1721)	wR2(reflections)= 0.1101(2018)	
<u>S = 1.101</u>	<u>N_{par}= 162</u>		

Table 2

Geometric parameters for hydrogen bonds and other intermolecular contacts operating in the crystal structure

<u>D-H...A</u>	<u>D-H</u>	<u>H...A</u>	<u>D...A</u>	<u>D-H...A</u>
N1-H30...O29 ⁱ	0.87(2)	2.080(19)	2.904(2)	157.4(16)
N1-H31...O3 ⁱⁱ	0.85(2)	2.07(2)	2.920(2)	177.5(18)
C26-H28...O3 ⁱⁱⁱ	0.97	2.59	3.462(3)	149

ⁱ: 1-x, 1-y, 1-z; ⁱⁱ: 1-x, -y, 1-z; ⁱⁱⁱ: 1/2-x, 1/2+y, 1/2-z.

Table 3

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

N1-C4	1.3580/1.3122	N1-H30	1.0066/0.8720
N1-H31	1.0084/0.8420	O2-C23	1.4157/1.4128
O2-C25	1.4181/1.4174	O3-C4	1.2181/1.2324
C4-C5	1.5457/1.5269	C5-H6	1.0943/0.9800
C5-N7	1.4665/1.4658	C5-C25	1.5306/1.5072
N7-C8	1.4774/1.4667	N7-C22	1.3713/1.3448
C8-H9	1.0896/0.9700	C8-H10	1.0929/0.9700
C8-C11	1.5156/1.5042	C11-C12	1.3973/1.3802
C11-C20	1.4012/1.3762	C12-H13	1.0857/0.9300
C12-C14	1.3956/1.3743	C14-H15	1.0842/0.9300
C14-C16	1.3922/1.3563	C16-H17	1.0842/0.9300
C16-C18	1.3960/1.3683	C18-H19	1.0844/0.9300
C18-C20	1.3919/1.3773	C20-H21	1.0846/0.9300
C22-C23	1.5269/1.4992	C22-O29	1.2229/1.2308
C23-H24	1.1002/0.9700	C23-H25	1.0901/0.9700
C26-H27	1.0887/0.9700	C26-H28	1.0989/0.9700

Bond angles (°)(DFT/XRD)

C4-N1-H30	121.3/120.4	C4-N1-H31	118.1/117.4
H30-N1-H31	119.2/122.0	C23-O2-C25	110.7/110.0
N1-C4-O3	123.6/123.4	N1-C4-C5	116.9/118.8
O3-C4-C5	119.5/117.8	C4-C5-H6	105.2/107.1
C4-C5-N7	114.5/114.2	C4-C5-C25	109.7/110.9
H6-C5-N7	108.5/107.1	H6-C5-C25	107.9/107.1
N7-C5-C25	110.6/110.0	C5-N7-C8	117.3/117.4
C5-N7-C22	123.2/122.6	C8-N7-C22	119.1/120.1
N7-C8-H9	106.5/109.1	N7-C8-H10	107.9/109.1
N7-C8-C11	113.3/112.6	H9-C8-H10	108.3/107.8
H9-C8-C11	110.5/109.1	H10-C8-C11	110.0/109.1
C8-C11-C12	120.8/120.8	C8-C11-C20	120.3/121.0
C12-C11-C20	118.9/118.2	C11-C12-H13	119.7/119.4
C11-C12-C14	120.7/121.2	H13-C12-C14	119.6/119.4

C12-C14-H15	119.8/120.0	C12-C14-C16	120.0/120.2
H15-C14-C16	120.2/120.0	C14-C16-H17	120.1/120.1
C14-C16-C18	119.7/119.8	H17-C16-C18	120.1/120.1
C16-C18-H19	120.0/119.7	C16-C18-C20	120.2/120.6
H19-C18-C20	119.8/119.7	C11-C20-C18	120.4/120.3
C11-C20-H21	119.4/119.9	C18-C20-H21	120.2/119.9
N7-C22-C23	117.2/118.2	N7-C22-O29	123.4/123.1
C23-C22-O29	119.4/118.7	O2-C23-C22	115.6/116.3
O2-C23-H24	110.9/108.2	O2-C23-H25	107.7/108.2
C22-C23-H24	106.7/108.2	C22-C23-H25	107.9/108.2
H24-C23-H25	107.9/107.4	O2-C26-C5	109.9/109.7
O2-C26-H27	107.7/109.7	O2-C26-H28	110.4/109.7
C5-C26-H27	109.8/109.7	C5-C26-H28	109.8/109.7
H27-C26-H28	109.2/108.2		

Dihedral angles (°)(DFT/XRD)

C26-O2-C23-C22	46.8/44.4	C23-O2-C26-C5	-67.0/-66.7
N1-C4-C5-N7	-15.9/-26.1	N1-C4-C5-C25	109.1/98.8
O3-C4-C5-N7	163.9/154.7	O3-C4-C5-C26	-71.1-80.4
C4-C5-N7-C8	-78.1/-74.5	C4-C5-N7-C22	109.7/106.0
C26-C5-N7-C8	157.4/160.0	C26-C5-N7-C22	-14.9/-19.5
C4-C5-C26-O2	-77.2/-73.9	N7-C5-C26-O2	50.1/53.5
C22-N7-C8-C11	99.5/131.1	C5-N7-C22-C23	-4.3/-1.7
C5-N7-C22-O29	174.8/177.5	C8-N7-C22-C23	-176.5/178.7
C8-N7-C22-O29	2.6/2.0	N7-C8-C11-C12	109.9/116.1
N7-C8-C11-C20	-70.3/-63.3	C8-C11-C12-C14	-180.0/-179.2
C20-C11-C12-C14	0.2/0.2	C8-C11-C20-C18	179.9/179.7
C16-C18-C20-C11	0.1/-0.1	N7-C22-C23-O2	-10.8/-10.1
O29-C22-C23-O2	170.0/170.6	C12-C11-C20-C18	-0.3/0.2
C12-C14-C16-C18	-0.2/1.0	C14-C16-C18-C20	0.1/-0.6
C11-C12-C14-C16	0.0/-0.8	C5-N7-C8-C11	-73.1/-48.5

Table 4

Calculated scaled wave numbers, observed IR, Raman bands and assignments of 4-benzyl-5-oxomorpholine-3-carbamide

B3LYP/6-311++G(d,p)(5D, 7F)			IR	Raman	Assignments ^a
$\nu(\text{cm}^{-1})$	IRI	RA	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3575	62.42	38.71	3550	-	$\nu\text{NH}_2(100)$
3450	35.08	156.28	3470	-	$\nu\text{NH}_2(100)$
3067	14.59	306.97	3070	3070	$\nu\text{CHI}(98)$
3058	14.04	21.86	3056	-	$\nu\text{CHI}(97)$
3051	9.43	84.36	-	3052	$\nu\text{CHI}(100)$
3042	0.45	75.09	-	3040	$\nu\text{CHI}(97)$
3034	6.02	37.89	3031	-	$\nu\text{CHI}(92)$
3011	4.96	79.50	-	-	$\nu\text{CH}_2(96)$
3000	2.09	45.42	3007	3008	$\nu\text{CH}_2(99)$
2995	6.32	110.86	2990	2980	$\nu\text{CH}_2(96)$
2941	15.67	139.88	-	2945	$\nu\text{CH}_2(90)$
2936	10.61	30.15	2933	-	$\nu\text{CH}(69), \nu\text{CH}_2(25)$
2878	47.54	123.71	2880	2888	$\nu\text{CH}_2(96)$
2872	19.98	80.40	2871	-	$\nu\text{CH}_2(97)$
1694	361.49	7.54	1694	1691	$\nu\text{C}=\text{O}(74)$
1655	346.31	13.21	1648	1660	$\nu\text{C}=\text{O}(78)$
1580	2.11	33.73	-	1590	$\nu\text{PhI}(56), \delta\text{CHI}(13)$
1561	1.47	9.87	1558	1563	$\nu\text{PhI}(69), \delta\text{CHI}(18)$
1540	128.44	3.19	1540	-	$\delta\text{NH}_2(84)$
1467	9.65	0.92	1467	1465	$\delta\text{CHI}(13), \nu\text{PhI}(60)$
1444	10.90	5.27	1447	-	$\delta\text{CH}_2(93)$
1430	16.56	8.35	-	-	$\delta\text{CH}_2(70)$
1428	8.36	1.15	-	-	$\delta\text{CHI}(17), \delta\text{CH}_2(18), \nu\text{PhI}(44)$
1415	2.69	12.05	1412	1418	$\delta\text{CH}_2(82)$
1392	103.84	2.90	1391	1390	$\nu\text{CN}(38), \delta\text{CH}_2(37)$
1347	3.19	2.00	1345	1348	$\delta\text{CH}_2(76)$
1332	14.54	6.11	-	-	$\delta\text{CH}_2(76)$
1315	41.81	1.49	-	-	$\nu\text{CN}(45), \delta\text{CH}_2(29), \nu\text{CC}(12)$
1314	13.25	1.30	1313	-	$\delta\text{CH}_2(43), \delta\text{CHI}(26)$

1305	12.74	3.22	-	1303	$\delta\text{CH}_2(45)$, $\delta\text{CHI}(20)$, $\nu\text{CN}(10)$
1295	39.34	1.53	-	-	$\delta\text{CH}(13)$, $\nu\text{PhI}(44)$, $\delta\text{CH}_2(18)$
1285	40.42	1.07	1288	1287	$\delta\text{CHI}(55)$, $\delta\text{CH}_2(15)$, $\nu\text{PhI}(12)$
1259	3.12	5.57	1257	1257	$\delta\text{CH}_2(45)$, $\delta\text{CHI}(13)$, $\nu\text{PhI}(22)$
1248	19.02	1.65	1245	1244	$\delta\text{CH}(19)$, $\delta\text{NH}_2(42)$
1219	138.57	7.42	-	1211	$\delta\text{CH}_2(25)$, $\nu\text{CN}(42)$
1196	20.00	5.88	1203	-	$\delta\text{CH}_2(56)$, $\nu\text{CC}(17)$, $\delta\text{CHI}(12)$
1175	5.38	22.18	1175	1174	$\nu\text{CC}(43)$, $\delta\text{CHI}(41)$
1158	0.61	3.93	1155	1157	$\delta\text{CHI}(78)$, $\nu\text{PhI}(14)$
1137	1.80	3.90	-	-	$\delta\text{CH}(72)$, $\nu\text{PhI}(15)$
1132	19.38	7.02	1133	1133	$\nu\text{CN}(36)$, $\delta\text{CH}_2(25)$
1108	76.67	1.29	1105	1113	$\nu\text{CO}(60)$
1070	24.19	1.35	1075	1070	$\delta\text{CH}_2(44)$, $\nu\text{CN}(15)$, $\nu\text{CO}(20)$
1064	17.01	0.90	-	-	$\nu\text{PhI}(31)$, $\delta\text{CHI}(58)$
1043	3.95	3.92	-	1039	$\delta\text{CH}_2(58)$, $\nu\text{CN}(17)$
1010	3.11	12.95	1012	1020	$\nu\text{PhI}(22)$, $\delta\text{PhI}(13)$, $\delta\text{CHI}(53)$
999	3.08	2.70	-	1003	$\delta\text{CH}_2(48)$, $\nu\text{CN}(11)$, $\nu\text{CC}(10)$
980	27.97	5.37	988	986	$\nu\text{CC}(42)$, $\nu\text{CN}(12)$, $\nu\text{CO}(11)$, $\delta\text{CH}_2(12)$
977	1.34	35.86	-	974	$\delta\text{PhI}(27)$, $\nu\text{PhI}(56)$
974	4.30	1.54	-	974	$\delta\text{CH}_2(28)$, $\nu\text{CC}(40)$
968	1.45	0.10	-	-	$\gamma\text{CHI}(83)$
953	0.27	0.05	955	953	$\gamma\text{CHI}(80)$
921	30.01	0.76	922	925	$\nu\text{CO}(35)$, $\delta\text{CH}_2(22)$
904	0.86	0.14	906	905	$\gamma\text{CHI}(60)$
874	14.46	1.56	870	870	$\delta\text{CH}_2(23)$, $\nu\text{CO}(10)$, $\nu\text{CC}(38)$
831	0.20	0.27	-	-	$\gamma\text{CHI}(89)$
828	3.99	2.10	830	825	$\delta\text{PhII}(26)$, $\delta\text{PhI}(15)$, $\gamma\text{CH}(34)$
799	5.09	14.17	798	797	$\nu\text{CC}(18)$, $\delta\text{C}=\text{O}(34)$, $\nu\text{PhI}(10)$, $\tau\text{PhI}(10)$
764	3.15	3.84	763	766	$\nu\text{CC}(34)$, $\nu\text{CN}(18)$, $\tau\text{PhI}(27)$
746	17.97	0.94	747	750	$\tau\text{PhI}(24)$, $\gamma\text{CHI}(15)$, $\gamma\text{CC}(18)$
711	3.59	13.07	-	-	$\gamma\text{C}=\text{O}(21)$, $\tau\text{NH}_2(10)$, $\delta\text{C}=\text{O}(31)$
691	51.88	0.58	698	695	$\tau\text{PhI}(18)$, $\gamma\text{CHI}(57)$

678	11.14	2.94	672	674	τ PhI(50), δ PhII(10)
610	0.36	4.12	612	608	δ PhI(85)
597	32.27	0.83	-	595	δ PhI(17), γ CN(22), τ PhI(10), δ CH ₂ (10)
588	1.26	1.82	-	582	τ NH ₂ (37), δ PhII(12)
561	11.75	1.41	-	558	γ C=O(43), δ CH ₂ (10), τ NH ₂ (10)
530	10.67	0.92	-	535	δ C=O(30), δ CH ₂ (21), δ PhI(18), δ PhII(13)
513	8.59	2.98	-	513	δ C=O(29), γ CC(13), τ NH ₂ (10), γ C=O(14)
487	12.46	1.11	-	490	δ PhII(28), τ NH ₂ (10), τ PhI(33)
472	13.00	2.94	-	-	τ PhI(24), γ CC(13), δ PhI(11), δ PhII(10)
418	8.32	0.42	-	420	τ PhI(34), δ C=O(14), γ CC(14)
399	0.10	0.04	-	404	τ PhI(83)
391	0.37	3.07	-	389	δ PhII(29), δ CN(10), τ PhII(10)
351	15.34	0.93	-	355	δ CC(16), δ CN(16), γ CN(13), τ PhII(11)
347	8.83	1.34	-	-	δ CC(15), τ PhII(14), γ CN(19), δ PhII(14)
333	58.14	0.97	-	-	γ CN(34), τ PhII(15), δ C=O(11)
315	123.13	0.12	-	318	γ CN(53), δ CO(12)
236	6.41	1.59	-	238	δ CC(23), δ CN(16), δ C=O(14)
217	1.97	1.12	-	-	τ PhII(45), τ PhI(13)
177	3.78	1.80	-	168	τ PhII(41), τ PhI(10), δ PhII(14)
149	2.16	1.31	-	144	γ CN(34), γ CC(11)
107	2.91	0.88	-	99	τ PhII(71), γ CN(10)
70	3.37	1.84	-	72	γ CN(34), τ PhII(56)
59	7.61	1.24	-	-	τ C=O(49), γ CN(10)
48	4.06	2.33	-	-	τ C=O(26), τ PhII(15), τ CH ₂ (18), τ CN(11), τ CC(11)
35	1.99	2.06	-	-	τ C=O(27), τ CH ₂ (26), τ PhII(26)
22	0.04	3.75	-	-	τ CN(55), τ CH ₂ (34)

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; phenyl and oxomorpholine rings are designated as PhI and PhII; potential energy distribution is given in brackets (%) in the assignment column.

Table 5

Simulated UV-visible absorption data of title molecule simulated in methanol obtained at TD-B3LYP/6-311++G(d,p) level of theory

TD-B3LYP/6-311++G(d,p)

Transitions	$\lambda_{\text{cal}}(\text{nm})$	f(a.u)	CI coefficient	Dominant contribution (%)
$S_0 \rightarrow S_1$	235	0.0001	0.4449	H-2 $\rightarrow$ L(40)
$S_0 \rightarrow S_2$	232	0.0032	0.3275	H $\rightarrow$ L(21)
$S_0 \rightarrow S_3$	225	0.0035	0.3968	H $\rightarrow$ L+2(31)
$S_0 \rightarrow S_4$	222	0.0192	0.5629	H $\rightarrow$ L(63)
$S_0 \rightarrow S_5$	215	0.0495	0.5631	H $\rightarrow$ L+1(63)
$S_0 \rightarrow S_6$	213	0.0356	0.4804	H-1 $\rightarrow$ L(46)
$S_0 \rightarrow S_7$	206	0.0111	0.4770	H-1 $\rightarrow$ L+2(46)
$S_0 \rightarrow S_8$	204	0.0053	0.4391	H $\rightarrow$ L+3(39)
$S_0 \rightarrow S_9$	203	0.0065	0.3406	H-3 $\rightarrow$ L(23)
$S_0 \rightarrow S_{10}$	201	0.0907	0.3261	H-3 $\rightarrow$ L+1(21)

Table 6 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(ij) ^c
O3-C4	σ	1.99447	C5-N7	σ^*	0.03799	1.03	1.37	0.034
O3-C4	π	1.99363	O3-C4	π^*	0.26858	1.22	0.43	0.022
-	-		C5-C26	σ^*	0.02953	1.11	0.74	0.026
C4-C5	σ	1.97418	N7-C22	σ^*	0.08472	1.17	1.10	0.032
C5-C26	σ	1.97391	O3-C4	π^*	0.26858	2.91	0.67	0.042
-	-		N7-C8	σ^*	0.03669	2.79	0.95	0.046
N7-C22	σ	1.98800	C5-N7	σ^*	0.03799	1.58	1.17	0.039
-	-		N7-C8	σ^*	0.03669	1.34	1.15	0.035
C8-C11	σ	1.97757	C11-C20	σ^*	0.02336	1.95	1.20	0.043
-	-		C12-C14	σ^*	0.01503	2.26	1.21	0.047
-	-		C18-C20	σ^*	0.01481	2.21	1.22	0.046
C22-C23	σ	1.98431	N7-C8	σ^*	0.03669	4.17	0.97	0.057
C22-O29	π	1.99380	C22-O29	π^*	0.30125	1.37	0.39	0.022
LPN1	σ	1.73690	O3-C4	σ^*	0.02097	1.05	0.86	0.029
-	-		O3-C4	π^*	0.26858	55.68	0.31	0.118
LPO2	σ	1.96633	C22-C23	σ^*	0.07145	2.24	0.94	0.041
-	π	1.92100	C5-C26	σ^*	0.02953	6.94	0.66	0.061
-	-		C22-C23	σ^*	0.07145	5.64	0.67	0.055
LPO3	σ	1.97652	N1-C4	σ^*	0.07034	1.90	1.14	0.042
-	-		C4-C5	σ^*	0.08829	2.18	1.02	0.043
-	-		N1-C4	σ^*	0.07034	25.52	0.72	0.123
-	-		C4-C5	σ^*	0.08829	22.19	0.59	0.104
LPN7	σ	1.67820	C4-C5	σ^*	0.08829	7.98	0.61	0.066
-	-		C8-C11	σ^*	0.02824	5.87	0.67	0.061
-	-		C22-O29	π^*	0.30125	65.38	0.28	0.120
LPO29	σ	1.97623	N7-C22	σ^*	0.08472	2.26	1.14	0.046
-	-		C22-C23	σ^*	0.07145	1.78	1.04	0.039
-	π	1.85570	N7-C22	σ^*	0.08472	25.78	0.71	0.123
-	-		C22-C23	σ^*	0.07145	20.73	0.61	0.102

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

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

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

Table 7 NBO results showing the formation of Lewis and non-Lewis orbitals.

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ O3-C4	1.99447	65.36	34.64	0.8085(sp ^{1.47})O+	40.40	59.60
-	-1.03720	-	-	0.5886(sp ^{2.15})C	31.75	69.25
π O3-C4	1.99363	69.88	30.12	0.8359(sp ^{65.67})O+	1.50	98.50
-	-0.38705	-	-	0.5488(sp ^{90.27})C	1.09	98.91
σ C4-C5	1.97418	47.75	52.25	0.6910(sp ^{1.86})C+	35.00	65.00
-	-0.63271	-	-	0.7228(sp ^{2.84})C	26.06	73.94
σ C5-C26	1.97391	52.48	47.52	0.7245(sp ^{2.69})C+	27.12	72.88
-	-0.63097	-	-	0.6893(sp ^{2.56})C	28.05	71.95
σ N7-C22	1.98800	63.56	36.44	0.7972(sp ^{1.79})N+	35.77	64.23
-	-0.83261	-	-	0.6037(sp ^{2.13})C	31.93	68.07
σ C8-C11	1.97757	49.68	50.32	0.7049(sp ^{2.45})C+	29.01	70.99
-	-0.62689	-	-	0.7094(sp ^{2.25})C	30.79	69.21
σ C22-C23	1.98431	49.66	50.34	0.7047(sp ^{1.84})C+	35.18	64.82
-	-0.64778	-	-	0.7095(sp ^{2.61})C	27.69	72.31
π C22-O29	1.99278	29.55	70.45	0.5436(sp ^{99.99})C+	0.30	99.70
-	-1.05386	-	-	0.8393(sp ^{99.99})O	0.39	99.61
n1N1	1.73690	-	-	sp ^{81.04}	1.22	98.78
-	-0.27216	-	-	-	-	-
n1O2	1.96633	-	-	sp ^{1.24}	44.56	55.44
-	-0.57644	-	-	-	-	-
n2O2	1.92100	-	-	sp ^{99.99}	0.05	99.95
-	-0.30194	-	-	-	-	-
n1O3	1.97652	-	-	sp ^{0.72}	58.06	41.94
-	-0.66796	-	-	-	-	-
n2O3	1.85735	-	-	sp ^{1.00}	0.00	100
-	-0.24186	-	-	-	-	-
n1N7	1.67820	-	-	sp ^{99.99}	0.34	99.66
-	-0.26103	-	-	-	-	-
n1O29	1.97623	-	-	sp ^{0.71}	58.34	41.66
-	-0.67394	-	-	-	-	-
n2O29	1.85570	-	-	sp ^{1.00}	0.01	99.99

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

Table 8**Mulliken atomic charges of title compound by B3LYP/6-311++G (d,p).**

<u>Atoms</u>	<u>Atomic charges</u>	<u>Atoms</u>	<u>Atomic charges</u>
O3	-0.297	H30	0.266
O29	-0.287	H31	0.339
N1	-0.438	H10	0.168
C4	0.185	H13	0.148
C22	0.170	H15	0.185
C16	-0.302	H17	0.156
C18	-0.377	H19	0.183
C20	-0.085	H21	0.192
C8	-0.768	H24	0.217
C23	-0.437	H25	0.213
C26	-0.402	H27	0.256
C5	-0.599	H28	0.155
C12	-0.317	H6	0.212
C14	-0.292	H9	0.250

Table 10Antibacterial activity of the title compound against bacterial pathogens

<u>Concentration of sample</u>	<u>Anti-bacterial activity (in mm)</u>			
(40 mg/mL)	<u>Gram positive</u>		<u>Gram negative</u>	
-	Pseudomonas	Escheria Coli	Bacillus	Bacillus
-	aureginosa	MTCC-1687	Cereus	Subtilis
-	MTCC-1035	-	MTCC-430	MTCC-441
Compound	10.3	16.6	12.0	17.5
Tetracycline (30µg/disc)	27.0	26.3	29.1	42.0
Control (10% DMSO)	-	-	-	-

Table 9 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	-7.5	0.000	0.000
2	-7.0	12.902	14.706
3	-6.8	13.418	15.485
4	-6.7	1.667	3.252
5	-6.5	2.683	4.393
6	-6.5	12.855	14.780
7	-6.4	2.677	4.552
8	-6.4	2.514	5.479
9	-6.4	13.366	15.535

Fig.1 FT-IR spectrum of 4-benzyl-5-oxomorpholine-3-carbamide

Fig.2 FT-Raman spectrum of 4-benzyl-5-oxomorpholine-3-carbamide

Fig.3a **Fig.3b** **Fig.3c****Fig.3 Hirshfeld surfaces of title compound**

Fig.4 ORTEP view of 4-benzyl-5-oxomorpholine-3-carbamide with thermal ellipsoids drawn at 50 % probability with optimized geometry

Fig.5. (a) Realization of $C_2^2(11)$ chains along $[010]$ from alternating $R_2^2(8)$ and $R_2^2(14)$ dimeric motifs (b) 1D $C_1^1(5)$ chains observed in the crystal structure when viewed down the a axis (c) Overall two dimensional architecture displayed by the title compound

Fig.6 UV-Vis spectrum (DFT) of 4-benzyl-5-oxomorpholine-3-carbamide

Fig.7 HOMO-LUMO plots of 4-benzyl-5-oxomorpholine-3-carbamide

Fig.8 MEP plot of 4-benzyl-5-oxomorpholine-3-carbamide

209.79 ALIE [kcal/mol] 366.94

Fig.9. Representative ALIE surface of 4-benzyl-5-oxomorpholine-3-carbamide

Scheme 1: **Preparation of 4-benzyl-5-oxomorpholine-3-carbamide**

Fig.10. Fukui functions of 4-benzyl-5-oxomorpholine-3-carbamide

Fig.11. BDE of all single acyclic bonds of 4-benzyl-5-oxomorpholine-3-carbamide

Bond	BDE [kcal/mol]
1	117.44
2	94.38
3	94.21
4	116.93
5	117.45
6	117.64
7	90.58
8	101.70
9	102.14
10	74.35
11	77.21
12	92.39

Fig.12. RDFs of a) carbon and b) non-carbon atoms with significant interactions with water

Fig.13 Pictorial representation with docked ligand embedded in the active site of pyrrole inhibitor with ten conformations

Fig.14 Schematic for the ligand interaction with H-bond surface of pyrrole inhibitor

Highlights

- XRD, IR, Raman spectral analysis were reported.
- Most reactive sites are predicted by using MEP plot
- BDEs are calculated to investigate autoxidation and degradation properties
- The compound might inhibitory activity against pyrrole inhibitor.