Molecular Crystals and Liquid Crystals

ISSN: 1542-1406 (Print) 1563-5287 (Online) Journal homepage: https://www.tandfonline.com/loi/gmcl20

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To cite this article: Gopal Sharma, Sumati Anthal, D. V. Geetha, Fares Hezam Al-Ostoot, Yasser Hussein Eissa Mohammed, Shaukath Ara Khanum, M. A. Sridhar & Rajni Kant (2018) Synthesis, structure and molecular docking analysis of an anticancer drug of N-(2-aminophenyl)-2-(2-isopropylphenoxy) acetamide, Molecular Crystals and Liquid Crystals, 675:1, 85-95, DOI: 10.1080/15421406.2019.1624051

To link to this article: https://doi.org/10.1080/15421406.2019.1624051

Published online: 27 Jun 2019.

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MOLECULAR CRYSTALS AND LIQUID CRYSTALS
2018, VOL. 675, NO. 1, 85–95
https://doi.org/10.1080/15421406.2019.1624051

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Synthesis, structure and molecular docking analysis of an anticancer drug of N-(2-aminophenyl)-2-(2-isopropylphenoxy) acetamide

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ABSTRACT

N-(2-aminophenyl)-2-(2-isopropylphenoxy) acetamide(**3**) has been synthesized in good yield by stirring compound ethyl 2-(2-isopropyl-phenoxy) acetic acid(**1**), with, 2-diaminobenzene (**2**), in dry dichloro-methane followed by the addition of lutidine, and TBTU in cooled condition. The crude product (**3**) was recrystallized and elucidated by elemental analyses and spectroscopic techniques (HNMR, LC-MS). The anticancer activity was confirmed by *in silico* modeling study which targets the VEGFr receptor. The compound crystallizes in the orthorhombic crystal system with space group Pbca with unit cell parameters: $a = 7.4250$ (4) Å, $b = 14.9753$ (7) Å, $c = 27.5656$ (14) Å and $Z = 4$. The crystal structure has been solved by using direct methods and refined by full matrix least-squares procédures to a final R-factor of 0.042 for 2158 observed reflections. The structure exhibits intermolecular H-bonds of the type N–H···O. In addition, two intramolecular interactions N1-H1 … O2 and N2-H2B … N1 were also observed.

KEYWORDS

Acetamide; Synthesis; X-ray diffraction; Direct Methods; Intermolecular interaction

1. Introduction

The field of drug discovery primarily deals with the design and synthesis of novel drugs, based on knowledge of how they work at the molecular level to target a specific gene [1]. Compounds with acetamide linkage exhibit a range of biological effects. Natural and synthetic acetamide derivatives display a variety of pharmacological applications, including antimicrobial [2, 3], antioxidant [4, 5] and anti-inflammatory [6, 7] activities. The applications of acetamide and analogs are, therefore, used as chemotherapeutic drugs and extensively studied [8]. Many derivatives of acetamide are used for the improvement of enzymes

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that prevent the replication of HIV virus activity [9]. Compounds of certain acetamide potentially inhibit the activity of farnesyl transferase enzyme, a major rule for the development novel potential anticancer drugs [10–13]. In addition, the computational biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational drug design helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor. The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor [14]. In view of the broad spectrum of biological properties and as a part of our ongoing work [15–17], the title compound was taken up for synthesized and structural characterization.

2. Materials and methods

2.1. Experimental

The chemicals were purchased from Sigma Aldrich and TCI Chemical Pvt. Ltd. TLC was performed on 0.25 mm silica gel plates (Merck 60 F_{254}) to ensure the progress and to monitor the reaction by using hexane: ethyl acetate (9:3)] system. Melting points and boiling point were measured on a Chemiline Cl725 melting point apparatus with a digital thermometer. ^{1}H NMR spectra were recorded on VNMRS-400 Agilent-NMR spectrophotometer in DMSO. Chemical shifts are given in parts per million downfield from tetramethylsilane. The mass spectra were obtained with a VG70-70H spectrophotometer and the elemental analysis (C, H) was performed on Elementar Vario EL III elemental analyzer. The results of elemental analyses were within ±0.4%.

2.1.1. Synthetic procedure for N-(2-aminophenyl)-2-(2-isopropylphenoxy) acetamide (3)

The synthesis of compound N-(2-aminophenyl)-2-(2-isopropylphenoxy) acetamide (**3**), was accomplished by the synthetic procedure shown in figure 1.

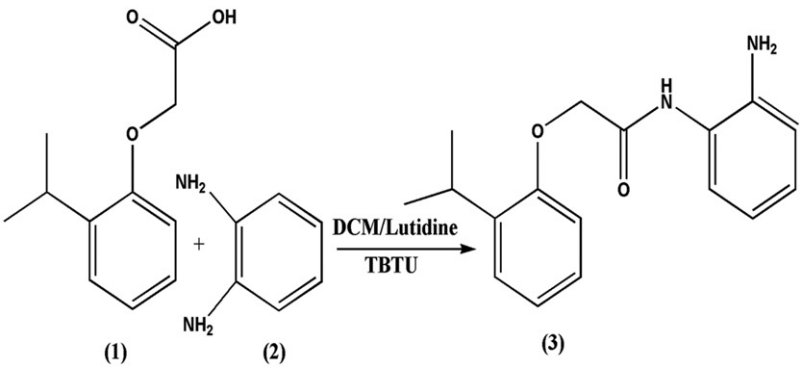

Figure 1. Schematic representation of the synthesis of the title compound (**3**).

To compound **1**, (0.8g, 0.009 mol), in dry dichloromethane (10 ml), lutidine (1.3 vol.) was added at 25-30 °C, followed by the addition of 1,2-diaminobenzene (**2**, 1.4g, 0.009 mol), The reaction mixture was stirred at 25-30 °C for 30 minutes. The reaction was cooled to 0-5 °C, TBTU (4.5g, 0.01 mol) was added over a period of 30 minutes while maintaining the temperature below 5 °C. The reaction was stirred overnight and monitored by TLC using mobile phase system [hexane: ethylacetate (9:3)]. The reaction mixture was diluted with 25 ml of dichloromethane and treated with 1.5N HCl solution (20 ml). The organic layer was washed with water (3 × 25 ml) and brine (3 × 25 ml). Finally, the organic layer was dried over anhydrous sodium sulfate and concentrated to obtain compound (**3**). The schematic spectrum of the synthesized compound is shown in figure 2.

2.2. Spectral data

2.2.1. N-(2-aminophenyl)-2-(2-isopropylphenoxy) acetamide (3)

Yield 80%; M.P.153-155 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ (ppm): 1.16 (d, 6H, $J = 8$ Hz, CH_3), 3.37 (m, H, CH), 4.70 (s, 2H, OCH_2), 4.85 (s, 2H, NH_2), 6.52-7.21 (m, 8H, Ar-H),

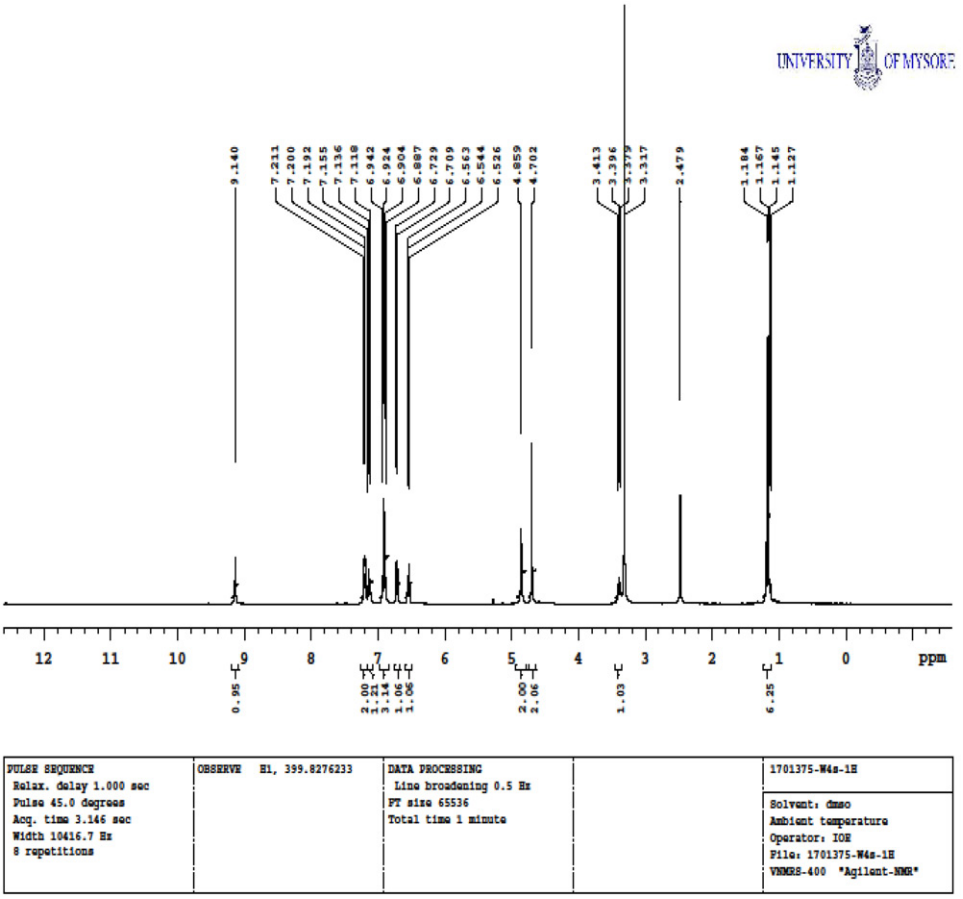

Figure 2. H NMR spectra of compound (**3**).

9.14 (s, 1H, NH); LC–MS m/z: 285 [M + 1]+. Anal. Calcd. for $C_{17}H_{20}N_2O_2$ (284): C, 71.81; H, 7.09. Found: C, 71.75; H, 7.00%.

2.3. Molecular docking studies

The synthesized molecule was subjected to molecular docking studies with ChemBioDraw Ultra 14.0 software which is used for building the structure of ligands. The compound used for docking was converted to 3D with ChemBio3D Ultra 14.0. For the purpose of *in silico*, autodock tools program was used. A conformational search of the ligand, which is considered in one of the applications of multi-conformer docking, was first approved, and all related low energy conformations were then inflexibly located in the binding site. In order to consider the rigid conformer, the rotational and translational degrees of freedom were allowed. A series of shape based filters were used by the autodock process and Gaussian shape fitting is the building block, in which scoring conformation depends on binding energies. By using autodock tools-1.5.6 the in silico study of the inhibitors with VEGFr kinase domain from VEGFr [PDB: 3qtk], were performed. Atomic coordinates of the proteins and ligands were downloaded and prepared for molecular docking. A method of Lamarckian genetic algorithm (LGA) was applied in the program which is used to identify the appropriate binding modes and conformation of the ligand molecules [18, 19].

2.4. X-ray intensity data collection, structure solution and structure refinement

X-ray intensity data of the crystal of dimensions 0.30 X 0.20 X 0.20 mm^3 was collected on *Bruker APEX2* CCD area-detector diffractometer [20] equipped with graphite monochromated Mo$K\alpha$ radiation (λ = 0.710 Å). X-ray intensity data of 33335 reflections were collected at 293(2)K and 3005 were found as unique. The intensities were measured by ω scan mode for θ ranging from 1.48 to 26°. A total number of 2158 reflections with $I > 2\sigma$ (I) were treated as observed. Data were corrected for Lorentz-polarization and absorption factors. The structure was solved by direct methods using SHELXS97 [21] and was refined using SHELXL97 [21]. All non-hydrogen atoms of the molecule were located from the best E-map. All the hydrogen atoms were geometrically fixed (except N2 and C14 hydrogen atoms) and allowed to ride on their parent carbon atoms with C—H= 0.93-0.97 Å, N—H = 0.86 Å. The final refinement cycles converged to an R-factor of 0.042 and $wR(F^2)$ = 0.148 for 2158 observed reflections. Residual electron densities ranges from -0.24 to 0.21 $eÅ^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables- 4.2.6.8 and 6.1.1.4). The geometry of the molecule was calculated using WinGX [22], PARST [23] and PLATON [24] softwares.

Crystallographic information (CIF) has been deposited at the Cambridge Crystallographic Data Centre with CCDC number 1906062. The crystallographic and refinement data of the crystal are presented in Table 1.

Table 1. Crystal data and other experimental details

CCDC Number	1906062
Crystal description	Block
Crystal size	0.30 x 0.20 x 0.20 mm^3
Empirical formula	$C_{17}H_{20}N_2O_2$
Formula weight	284.35
Radiation, Wavelength	Mo $K\alpha$, 0.71073 Å
Unit cell dimensions	a = 7.4250 (4) Å , b = 14.9753 (7) Å, c = 27.5656 (14) Å
Crystal system, Space group	Orthorhombic, *Pbca*
Unit cell volume	3065.1 (3) $Å^3$
No. of molecules per unit cell, Z	8
Absorption coefficient	0.08 mm^{-1}
F(000)	1215.8
θ range for entire data collection	1.48 to 26.00
Reflections collected / unique	33335/3005
Reflections observed I > 2σ(I))	2158
Range of indices	h=-8 to 9, k=-17 to 18, l= -34 to 34
No. of parameters refined	208
Final R-factor	0.042
wR(F^2)	0.148
Rint	0.033
Goodness-of-fit	1.082
Final residual electron density	$-0.24< \Delta\rho >0.21 eÅ^{-3}$
Measurement	Bruker APEX-II CCD
Software for structure solution:	SHELXS97
Software for refinement	SHELXL97
Software for molecular plotting	ORTEP PLATON Mercury

3. Results and discussion

3.1. In silico validation

The autodock program was utilized to produce the protein-tested compound complex, in order to understand the interaction between VEGFr protein and ligand. It can be seen clearly in figure 3 that ligand is placed in the center of the active site and it is stabilizedby hydrogen bonding interactions. The hydrogen bonds exhibited in the VEGFr-tested compound complex have been documented, together with their distances and angles, by taking into account the interaction energies of the tested compound with residues in the active site of the VEGFr, key binding residues in the active site of the model were determined and proved. It is obvious that the VEGFr-tested compound complex has substantial binding energy of -6.24 kJ/mol. Also, it was shown by the interaction analysis that ILE22, the amino acid residue of the VEGFr, were the main providers for the inhibitory interaction figure 3.

3.2. In Single crystal XRD

The molecular structure containing atomic labelling is shown in Figure 4 (ORTEP) [25].

The dihedral angle between the benzene ring A and B is 39.72°. Some selected bond distances, bond angles and torsion angles which play an important role in collating the structural properties of this molecule are presented in Table 2. Bond distances and angles are within normal range [26] and the C = O and N—H bond distances are

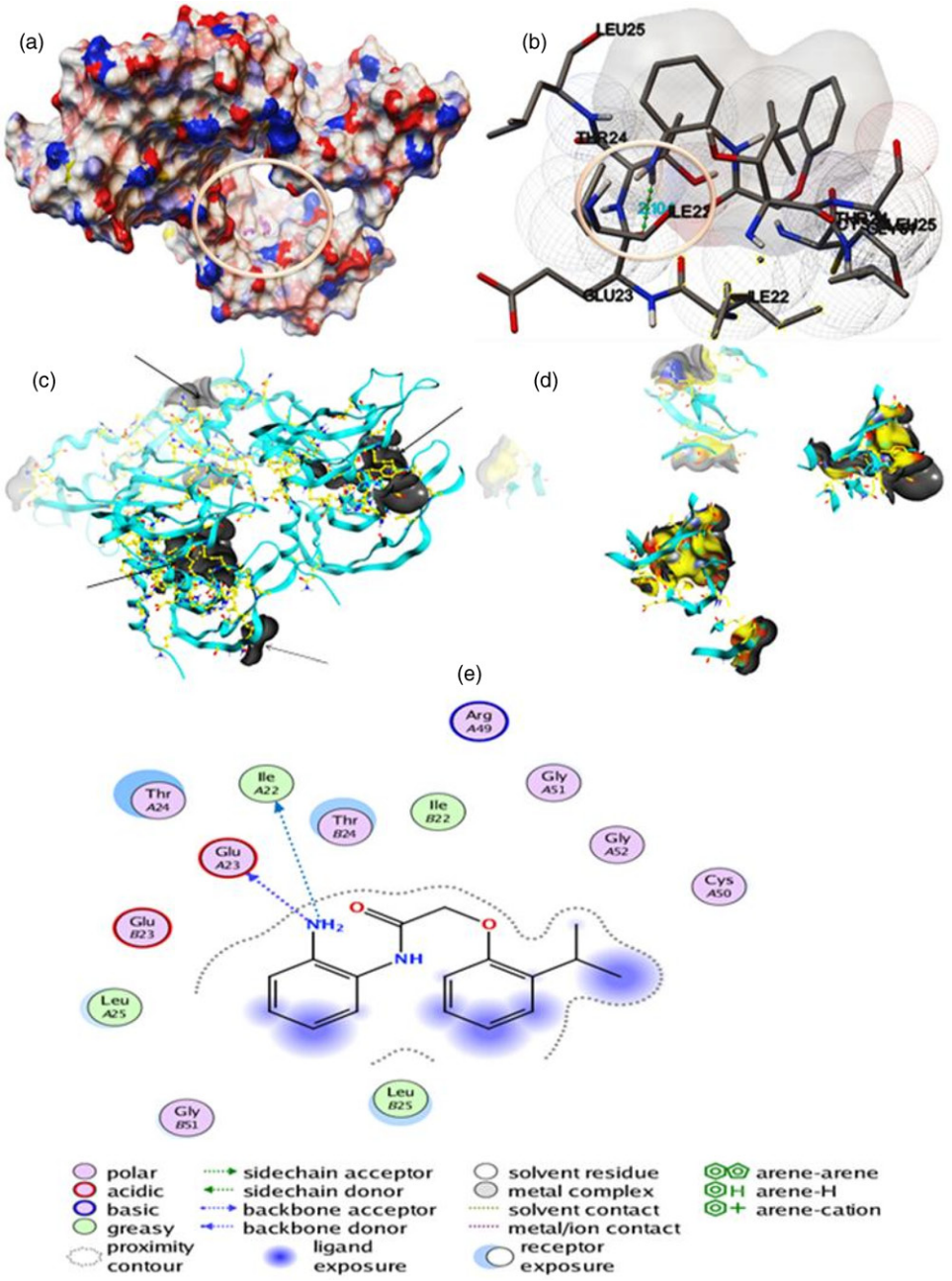

Figure 3. *In silico* interaction of tested compound with VEGFr as the basis for cancer regression. **a)** Enfolding of tested molecule in the active site pocket of VEGFr complex. **b)** Hydrogen bond interaction of the ligand with VEGFr. **c)** Ribbon models of the VEGFr catalytic domain. **d)** The pocket sits interaction with the ligand molecule. **e)** 2D interactions analysis of the tested compound with VEGFr.

Table 2. Selected bond distances, bond angles and torsion angles.

Bond Distances (Å)		Bond Distances (Å)	
N1—C7	1.338 (2)	C14—13	1.509 (3)
N2—C1	1.382 (2)	C14—C16	1.520 (3)
O1—C7	1.2252 (19)	C14—C17	1.524 (3)
O2—C8	1.376 (2)	C15—C7	1.501 (2)
O2—C15	1.418 (2)	N1—C6	1.430 (2)
Bond Angles(°)		Bond Angles(°)	
C2—C1—C6	118.00 (15)	O2—C8—C13	115.09 (16)
N2—C1—C2	120.16 (17)	C8—C13—C14	120.25 (16)
C1—C6—N1	118.89 (15)	C12—C13—C14	123.33 (19)
N2—C1—C6	121.81 (16)	C13—C14—C16	110.82 (18)
C5—C6—N1	120.62 (15)	C13—C14—C17	114.33 (18)
N1—C7—C15	116.91 (14)	C16—C14—C17	110.25 (18)
O1—C7—C15	119.00 (14)	O2—C15—C7	110.26 (13)
O1—C7—N1	124.08 (16)	C7—N1—C6	124.50 (15)
C9—C8—C13	121.68 (17)	C8—O2—C15	117.88 (13)
O2—C8—C9	123.23 (17)		
Torsion Angles (°)		Torsion Angles (°)	
C16—C14—C13—C12	102.4 (2)	C16—C14—C13—C8	−77.2 (2)
C17—C14—C13—C12	−23.0 (3)	C17—C14—C13—C8	157.45 (18)
O2—C15—C7—O1	167.84 (16)	O2—C15—C7—N1	−11.7 (2)
C7—N1—C6—C5	51.5 (2)	C7—N1—C6—C1	−130.10 (18)

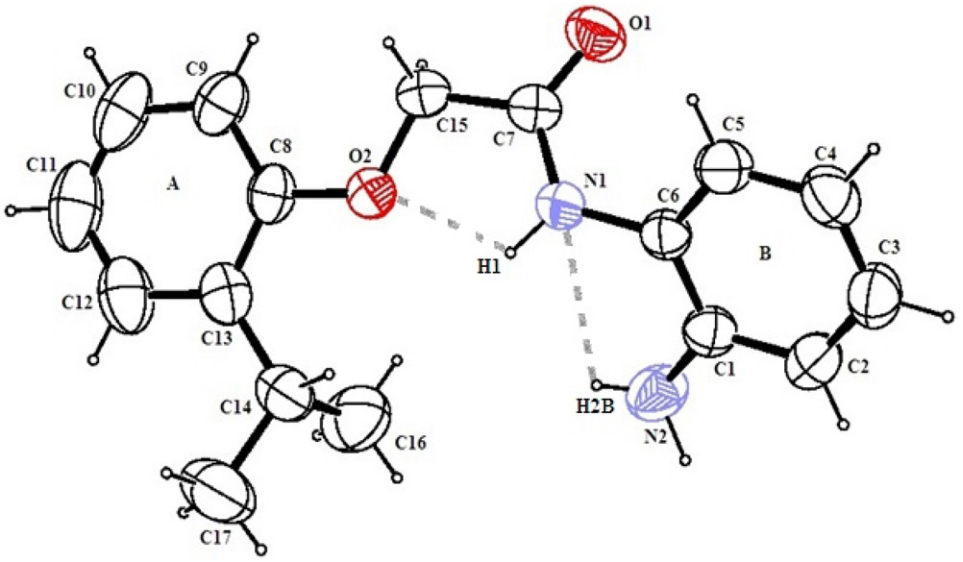

Figure 4. ORTEP view of the molecules with displacement ellipsoids at the 40% probability level. H atoms shown as small spheres of arbitary radii.

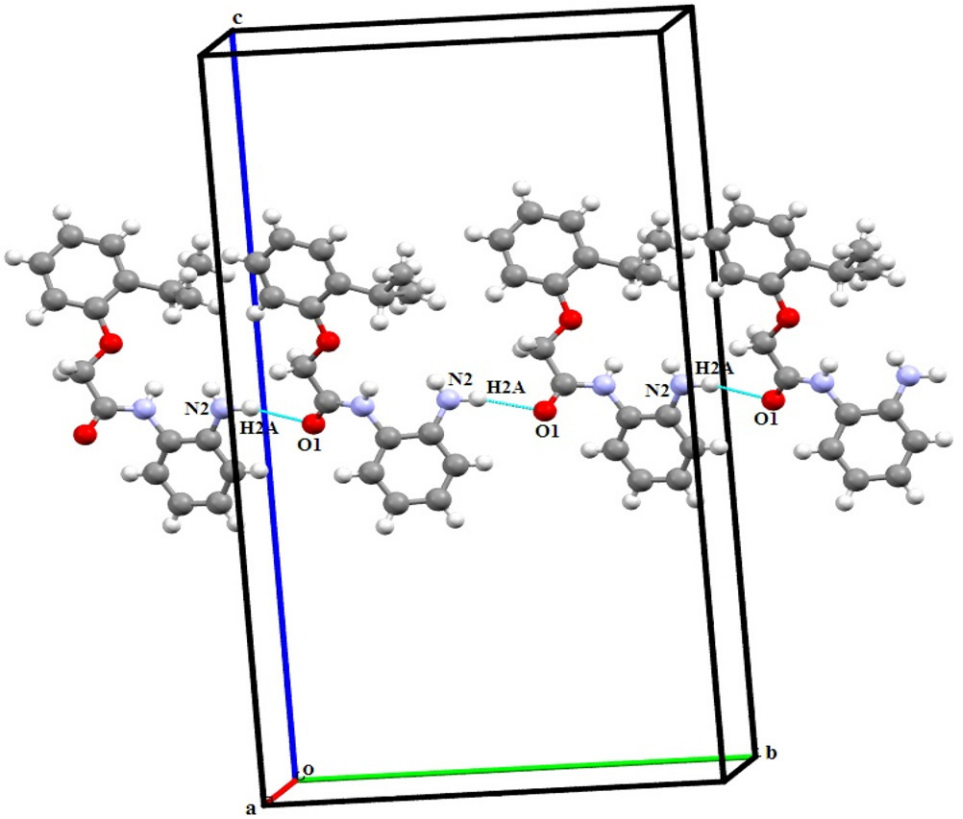

Figure 5. Intermolecular hydrogen bonds linking the molecule along ***b***-axis.

comparable with the values observed for some analogous structures [27, 28]. Rings A and B are essentially planar, with atom C8 and C3 displaced out of their mean ring planes by 0.0094Å and 0.0048Å, respectively. The N2 atom attached with the carbon atom C1 is coplanar with the ring B and the same is vindicated by the magnitude of torsion present in angles N2—C1—C2—C3 = 177.57(18)° and C5—C6—C1—N2 = -178.36(17)°, respectively.

In the crystal structure, there exists two intramolecular hydrogen bonds, viz. N1-H1 … O2 and N2—H2B … N1, and these results in a formation of a five- membered ring with graph-set motif S(5) [Figure 4]. It is worth mentioning that, the molecular packing inthe crystal structure is stabilized by intermolecular hydrogen bond [N2—H2A … O1] that links the molecules into chains along b-axis is shown in Figure 5 (Mercury) [29]. Molecular packing in the unit cell viewed down the a-axis is shown in Figure 6 (PLATON) [24]. The details of intra/inter-molecular hydrogen bonds are given in Table 3.

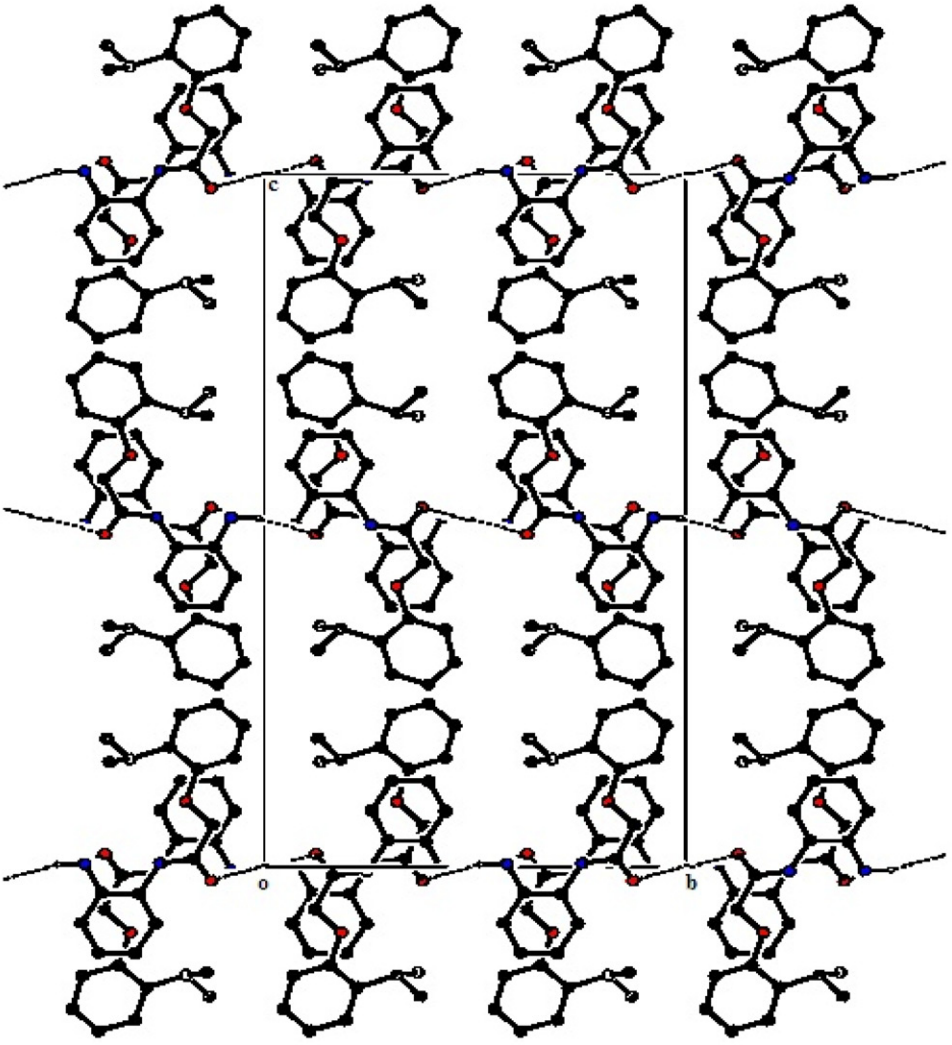

Figure 6. Packing of the molecules as viewed down the ***a***-axis.

Table 3. Hydrogen bonding geometry (e.s.d.'s in parentheses)

D–H … A	D–H(Å)	H … A(Å)	D … A(Å)	D–H … A(°)
N1—H1 … O2	0.85	2.18	2.6141	111
N2—H2B … N1	0.80	2.53	2.8186	103
N2—H2A … O1^{i}	0.94	2.23	3.1423	163

Symmetry code: (i) 1/2 - X, -1/2 + Y, Z

Acknowledgments

R. K is thankful to the Department of Science and Technology, New Delhi for funding under sponsored Research Project (No. EMR/2014/000467). Geetha thanks UGC BSR-RFSMS for a fellowship. Fares Hezam Al-Ostoot thanks the Government of Yemen and Albaidha University, Yemen, for the financial assistance. Shaukath Ara Khanum acknowledges the support provided by VGST, Bangalore, under CISEE Program [Project sanction order: No. VGST/CISEE/282].

Yasser Hussein Eissa Mohammed thanks the University of Hajjah, Yemen, for providing financial assistance under the teacher's fellowship.

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