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Crystal Structure and Hirshfeld Surfaces of 5-(3-Bromophenyl)-3-(4-methoxyphenyl) Isoxazole

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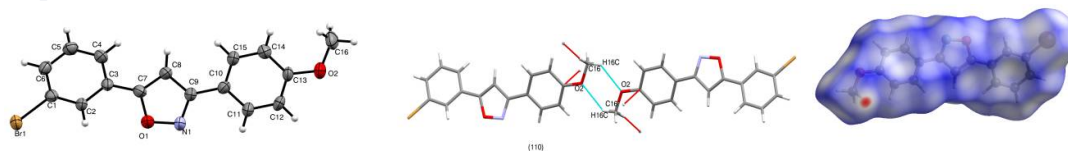
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ABSTRACT

The titled compound was synthesized and the structure was investigated by X-ray crystallography. The compound crystallizes into a monoclinic crystal class with space group of $P_{21/c}$ with unit cell parameters of $a=30.1197(19)\text{\AA}$, $b=5.8661(4)\text{\AA}$, $c=7.7258(5)\text{\AA}$, $\beta=96.630(3)^\circ$ and $Z=4$. The structure is solved by a direct method and it is refined to $R_1=0.053$. The dihedral angle between the terminal benzene rings are $48.3(2)^\circ$ which indicate the structure is not a planar one. The presence of C-H... π and C-H...O intermolecular interactions leads to the formation of molecular stacking parallel to (101) plane. The Hirshfeld surface studies were carried out and it is confirmed that C...H, H...H and H...Br are the significant contributions towards packing.

Graphical Abstract



Keywords: Isoxazole, Dihedral angle, C-H... π interactions, Hirshfeld surfaces.

INTRODUCTION

Isoxazole is one of the important type of heterocycles containing nitrogen atom next to the oxygen atom and is commonly found in some natural products, such as muscimol and ibotenic acid. The wide literature survey reveals that isoxazole and its derivatives have great importance in the field of organic chemistry and medicine since it possesses various biological activities such as anti-tumour, antioxidant, antimicrobial, anti-psychotic anticonvulsant, antidepressant [1-2], hence isoxazole derivatives represent a key structural design in most of the biologically active molecules. The biological activities of compound has closer relationship to their electronic property, hence the substitution of electron withdrawing groups such as chloro, bromo and nitro groups on benzene ring

exhibited more activity than without substitution on benzene ring [3], the recent literature survey showed that substitution of methyl or methoxy groups to the benzene ring reported to exhibited better antibacterial and anti-fungal activities compared to other substituted compounds [4]. In addition to this, usage of traditional non steroidal anti-inflammatory drugs leads to the severe side effects such as kidney failure, ulcers and extended bleeding after a surgery or an injury, also the compound 5-(3-methylthiophene-2yl)-3-(3,4,5-trimethoxyphenyl)isoxazole reported as a potential inhibition of anti-inflammatory enzymes [5]. In the view of above mentioned various significant biological activities and in continuation of our work on isoxazole derivatives [6], the crystal structure and Hirshfeld surfaces for the compound 5-(3-Bromophenyl)-3-(4-methoxyphenyl) isoxazole is hereby reported.

MATERIALS AND METHODS

The cyclo addition reaction of 4-methoxybenzaldehyde (3.4g, 25mmol), hydroxylamine hydrochloride (1.40g, 20mmol), chloramine-T trihydrate (4.55g, 20mmol) and 1-bromo-3-ethynylbenzene (5.40g, 30mmol) yields a white colored solid. A block shaped crystal of 5-(3-bromophenyl)-3-(4-methoxyphenyl) isoxazole were grown from ethylacetate solvent by slow evaporation technique at room temperature [7]. The schematic diagram of the molecule is shown in figure 1.

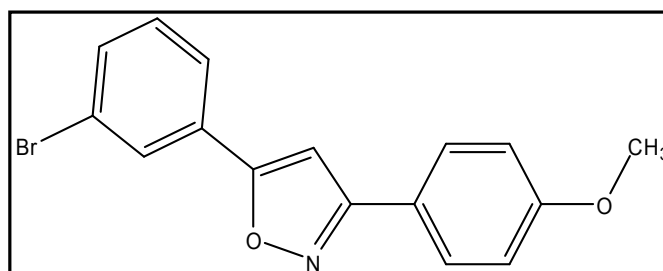


Figure 1. Chemical diagram of the compound.

A single crystal of suitable size were selected for X-ray diffraction study, the diffraction data were collected on a Apex Bruker-II diffractometer using MoK α monochromated radiation ($\lambda = 0.71073 \text{ \AA}$). A complete intensity data set was processed using SAINT. The crystal structure was solved by a direct method using the program SHELXS-97 and refined by the procedure of full matrix least squares based on F^2 SHELXL-97 [8-10], all non-hydrogen atoms refined anisotropically, whereas hydrogen atoms were placed at chemically allowed positions and refined as a riding model with

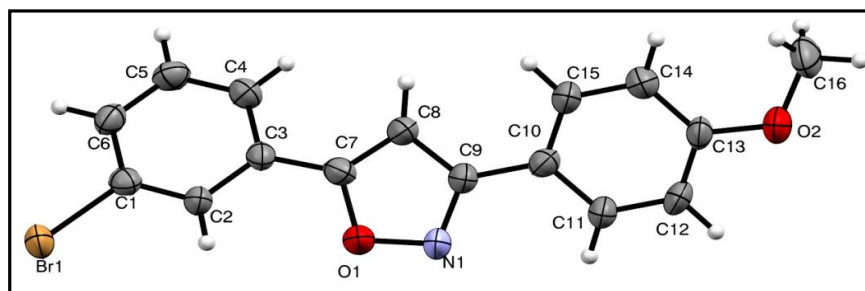


Figure 2. ORTEP drawing of the ligand with thermal ellipsoids drawn at 50% of the probability.

isotropic displacement parameters set as $C-H=0.93 \text{ \AA}$ with $U_{iso}(H)=1.2U_{eq}(C)$ for aromatic rings and $C-H=0.96 \text{ \AA}$ with $U_{iso}=1.5U_{eq}(C)$ for methyl group, after several cycles of refinement, the structure is converged to the $R_1=0.053$. All the geometric parameters were calculated using PLATON [11]

software and MERCURY [12] software is used for generating ORTEP (Figure 2) and packing diagrams.

The Hirshfeld surface is an effective tool, it is extensively used to analyze nature of inter-molecular interactions and to quantify its percentage of contribution by two dimensional fingerprint plots. It is obtained by submitting crystallographic information file (.cif) into Crystal Explorer 3.1 software [13-15]. A three-dimensional Hirshfeld surface is mapped over d_{norm} (normalized contact distance) surface between the color scheme of (-0.1160 au) for blue and (+0.9712 au) for red, also it is made transparent to visualize arrangement of all the atoms in a molecule.

RESULTS AND DISCUSSION

The titled compound is crystallized into a monoclinic lattice system with the space group of $P_{21/c}$, the relevant crystal and refinement data is summarized in table 1. The bond lengths and bond angles are in good agreement with previously reported compounds [16-18]. The selected bond lengths, bond angles and torsion angles are listed in table 2, 3 and 4 respectively.

Table 1. Crystal and refinement data

CCDC Number	CCDC-1838090	No. of reflections measured	6618
Chemical formula	$C_{16}H_{12}BrNO_2$	No. of independent reflections	2321
Molecular weight	330.18	No. of reflections observed	1544
Density	1.617 Mg m^{-3}	R_{int}	0.053
Crystal system, space group	Monoclinic, $P_{21/c}$	Data /restraints/parameters	2321/0/183
Temperature	290 K	$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$	0.69, -0.85($e \text{ \AA}^{-3}$)
Crystal size	$0.30 \times 0.25 \times 0.20 \text{ mm}^3$	Refinement method	Full matrix least squares
Unit cell dimensions	$a=30.1197(19) \text{ \AA}$, $b=5.8661(4) \text{ \AA}$, $c=7.7258(5) \text{ \AA}$, $\beta=96.630(3)^\circ$	Goodness-of-fit on F^2	1.05
Volume and Z	$1355.91(15) \text{ \AA}^3$ and 4	Final R indices	$R_1=0.053$, $wR_2=0.116$
Radiation type and wavelength	MoK α , 0.71073 \AA	$F_{(000)}$	664
Absorption co-efficient	3.03 mm^{-1}	Index ranges	$h = -31 \rightarrow 35$, $k = -6 \rightarrow 6$, $l = -8 \rightarrow 8$
Absorption correction	psi-scan	Theta range for data collection	2.6 to 25.1°
Tmin, Tmax	0.419, 0.545		

Table 2. Selected bond lengths (\AA)

Atoms	Length	Atoms	Length
O2-C13	1.375(7)	C3-C7	1.450(8)
O2-C16	1.433(7)	C8-C9	1.425(7)
C2-C3	1.410(6)	C10-C9	1.465(8)
C9-N1	1.330(5)	C1-Br1	1.912(5)
C7-O1	1.369(5)	C3-C4	1.408(6)
N1-O1	1.406(7)	C3-C7	1.450(8)

The molecular structure comprises 3-bromophenyl and 4-methoxyphenyl rings are linked to fifth and third position of an isoxazole ring. The inter-planar angle between 3-bromophenyl ring and 4-methoxy phenyl ring is $48.3(2)^\circ$ which indicates that the structure is not a planar one, but they are twisted with respect to mean plane of five-membered isoxazole ring. The dihedral angle of an isoxazole ring (O1-N1-C7-C8-C9) with bromo-substituted benzene ring (C1-C2-C3-C4-C5-C6) is $23.9(3)^\circ$ while that of with methoxy-substituted benzene ring (C10-C11-C12-C13-C14-C15) is $26.5(3)^\circ$ which is slightly higher depends on a pattern of intermolecular hydrogen bond interaction of the type C16-H16...O2 since O2 of a neighboring molecule acts as a donor. The methoxy group

substituted at C13 position of a phenyl ring is in *-syn-periplanar* conformation defined by a torsion angle value of $-9.5(7)^\circ$ for the atoms (C14-C13-O2-C16).

Table 3. Selected bond angles ($^\circ$)

Atoms	Angles	Atoms	Angles
C13-O2-C16	119.0(4)	C11-C10-C15	117.5(5)
C2-C1-C6	122.2(5)	C11-C10-C9	121.2(4)
C2-C1-Br1	119.8(3)	C15-C10-C9	121.3(4)
C6-C1-Br1	118.0(4)	C5-C6-C1	118.9(5)
O2-C13-C14	125.6(4)	C15-C14-C13	119.8(4)
O2-C13-C12	115.4(4)	N1-C9-C8	110.8(5)
C2-C3-C7	122.2(4)	N1-C9-C10	120.6(5)
C7-C8-C9	105.6(4)	C8-C9-C10	128.6(4)
C5-C4-C3	121.0(4)	C8-C7-O1	109.0(5)
C9-N1-O1	105.6(4)	C8-C7-C3	133.3(4)
C7-O1-N1	109.1(3)	O1-C7-C3	117.8(4)

Table 4. Selected torsion angles ($^\circ$)

Atoms	Angles	Atoms	Angles
C16-O2-C13-C14	$-9.5(7)$	C11-C10-C9-N1	$25.3(7)$
C16-O2-C13-C12	$171.1(4)$	C15-C10-C9-N1	$-154.9(4)$
C1-C2-C3-C4	$-1.2(6)$	C9-C8-C7-O1	$0.5(5)$
C1-C2-C3-C7	$176.9(4)$	C4-C3-C7-C8	$22.9(7)$
C7-C3-C4-C5	$-177.7(4)$	C3-C7-O1-N1	$179.6(4)$
O2-C13-C12-C11	$178.4(5)$	C4-C3-C7-O1	$-157.3(4)$
C3-C2-C1-Br1	$179.8(3)$	C2-C3-C7-O1	$24.5(6)$
C5-C6-C1-Br1	$-178.5(3)$	C8-C9-N1-O1	$-0.1(5)$
O2-C13-C14-C15	$-179.2(4)$	C10-C9-N1-O1	$-178.2(4)$
C7-C8-C9-N1	$-0.3(5)$	C9-N1-O1-C7	$0.4(5)$

The C-C bond lengths within the benzene rings are in the range from $1.356(8)\text{\AA}$ to $1.410(6)\text{\AA}$ is bit large but consistent with the aromatic character of the ring system [19-20] and their endocyclic bond angles varies from $118.5(5)^\circ$ to $122.2(5)^\circ$ with a mean value of $120.4(5)^\circ$ which is coinciding with theoretical value of 120° for sp^2 hybridization [21]. Further the bond angle of $125.6(4)^\circ$ for the atoms (O2-C13-C14) is larger than the bond angle value of $115.4(2)^\circ$ for the atoms (O2-C13-C12) which is due to the repulsion of methyl group from -CH of a phenyl ring system and leads to intra-molecular interactions.

In the crystal structure adjacent molecules are bounded into inverted dimers through intermolecular interaction of the type C16-H16...O2 and forms into a closed loop of $R_2^2(6)$ as shown in figure 3. The structure also exhibited C-H... π interactions through C5-H5...Cg2 (Figure 4) Cg2 is the centroid of the ring (C1-C2-C3-C4-C5-C6) with a C-Cg distance of $3.563(6)\text{\AA}$, H...Cg distance of 2.90\AA , C-H...Cg angle of 130° with a symmetry code $x, -1/2-y, 1/2+z$ and C11-H11...Cg3; where Cg3 is the centroid of the ring (C10-C11-C12-C13-C14-C15) with a C-Cg distance of $3.575(5)\text{\AA}$, H...Cg distance of 2.97\AA , C-H...Cg angle of 125° with a symmetry code $x, 1/2-y, 1/2+z$. The stacking of molecules lying parallel to (101) plane through the intermolecular interaction of the type C-H...O are observed as shown in figure 5.

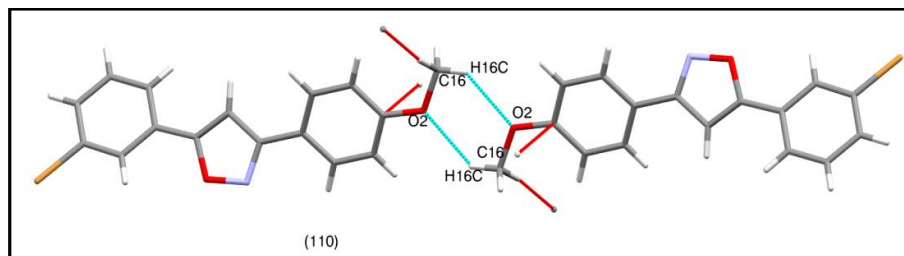


Figure 3. Visualization of $R_2^2(6)$ ring motif viewed along (110) plane through C-H...O intermolecular interactions.

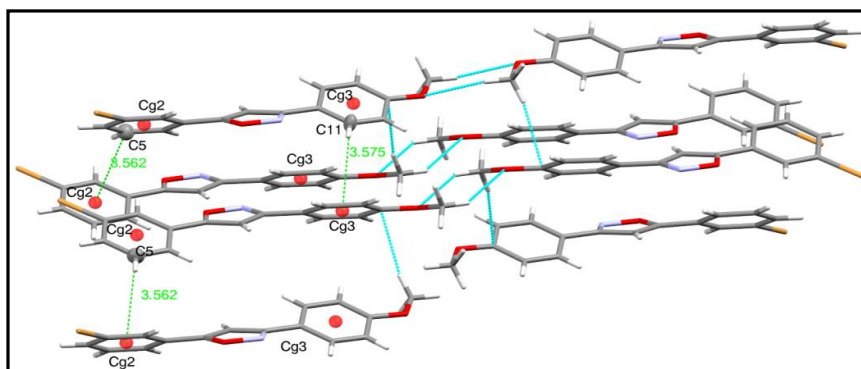


Figure 4. Visualization of C-H... π interaction, only for few molecules are shown and the hanging contacts are removed for clarity purpose.

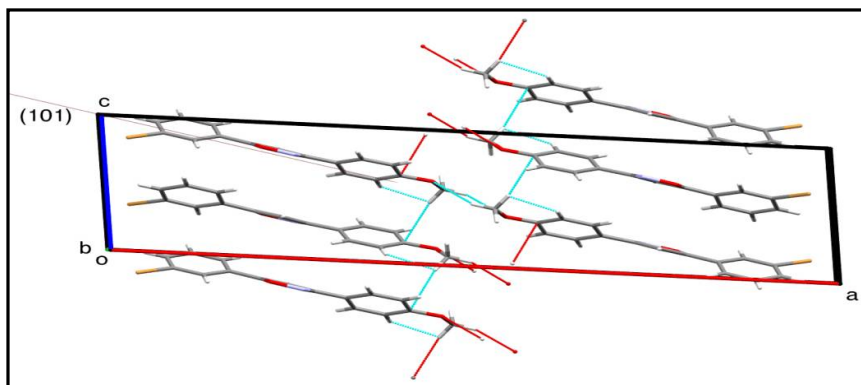


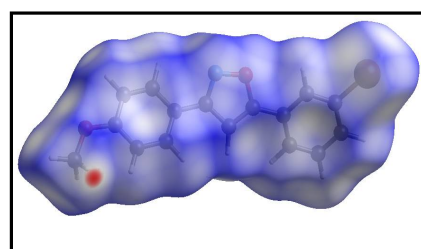
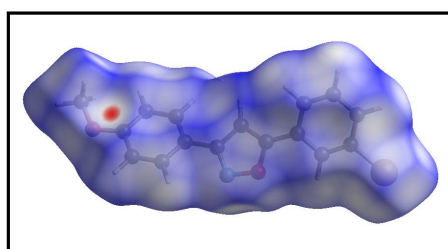
Figure 5. Packing of the diagram when it is viewed along c axis, molecules stack layers lying parallel to (101) plane through intermolecular interactions of the type C-H...O and intramolecular interactions are indicated in dotted lines.

The area and volume of three dimensional Hirshfeld surface mapped over d_{norm} surface are 316.93\AA^2 and 331.91\AA^3 is shown in figure 6a. The Hirshfeld surface is characterized by dark red spots nearby the atoms C16 and O2. It reveals that the active participation of the respective atoms in the intermolecular interactions of the type C-H...O which is discussed in X-ray diffraction study. The two-dimensional fingerprint plots are depicted in figure 6b (i-v). A pair of inter-atomic C...H contacts appeared as a blue colored distinct curved spikes over the region of $1.02\text{\AA} < (d_e + d_i) < 1.58\text{\AA}$ with the highest contribution of 31.6%, followed by 29.7% for H...H contacts appeared as a blue colored spikes merged almost in the same length over the region of $1.18\text{\AA} < (d_e + d_i) < 1.19\text{\AA}$. The H-Br contacts

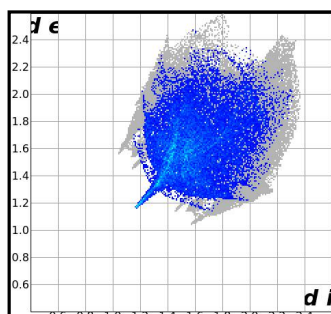
are indicated as blue colored wings in the region of $1.18\text{\AA} < (d_e + d_i) < 1.90\text{\AA}$ with the contribution of 12.4%. The contributions of H...O and H...N are 10.1% and 4.4% reflected as a pair of blunt spikes over the regions $1.10\text{\AA} < (d_e + d_i) < 1.48\text{\AA}$ and $1.15\text{\AA} < (d_e + d_i) < 1.55\text{\AA}$ respectively, apart from these other pair of contacts present with contribution less than 4% they are summarized in table 5. The full contribution is shown in figure 6b(vi).

Table 5. Summary of inter-atomic contacts and their percentage of contribution towards Hirshfeld surface.

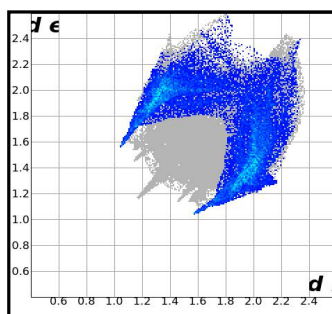
Pair of contact	Contribution	Pair of contact	Contribution
Br...Br	3.2	C...Br	0.8
C...N	3.1	O...N	0.4
C...O	2.9	O...O	0.2
C...C	1.1	N...N	0.1



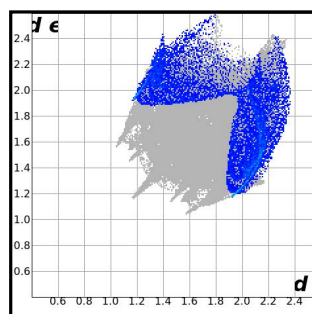
(a)



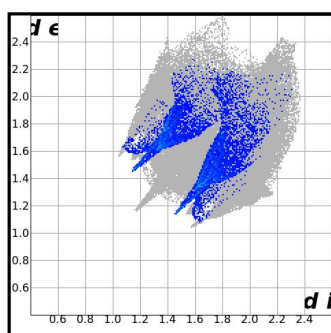
(i) C-H (31.6%)



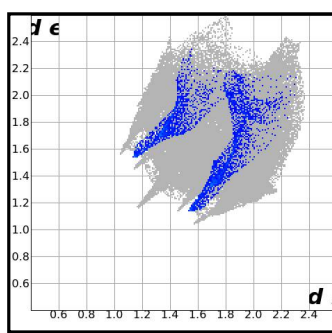
(ii) H-H (29.7%)



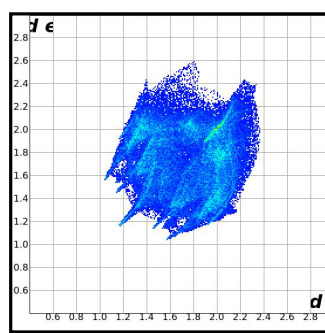
(iii) H-Br (12.4%)



(iv) H-O (10.1%)



(v) H-N (4.4%)



(vi) Full

(b)

Figure 6 : (a) The 3D Hirshfeld surface, the red spots on d_{norm} surface indicate participation of intermolecular interactions of type C-H...O. (b) (i – v) Two dimensional fingerprint plots of various interactions in terms of percentage and (vi) indicate full.

APPLICATION

Precise measurement of bond lengths, bond angles and torsion angles.

CONCLUSIONS

The compound is crystallized into a monoclinic system with the space group $P_{21/c}$, structure is not a planar but it is twisted with respect to an isoxazole ring system. The molecular structure is stabilized with intermolecular interaction of the type C-H...O. The structure is also displayed C-H... π interaction with the bond length range of 3.563(6)Å to 3.575(5)Å hence it will have the good scope for carrying out study of biological activities. Further the Hirshfeld surface studies confirmed that C...H, H...H and H...Br contacts are the major contributions towards packing of Hirshfeld surface.

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