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Crystal Structure, Molecular Docking, Hirshfeld Surfaces and Computational Studies of (2-((1H-Benzo[D]Imidazol-2-Yl) Methoxy)-5-Chlorophenyl)(4-Chlorophenyl)Methanone

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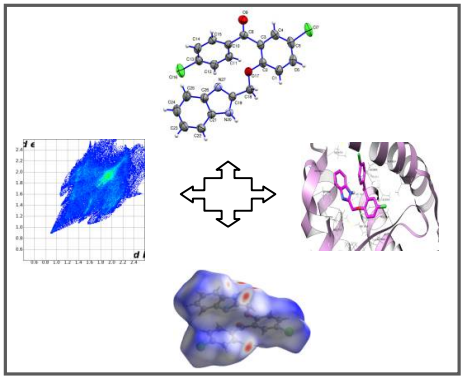
ABSTRACT

The title compound was synthesized and characterized by single crystal X-ray diffraction studies, molecular docking and Hirshfeld surface analysis. The title compound $C_{21}H_{14}N_2O_2Cl_2$ crystallizes in the monoclinic system with the space group of $P2_{1/c}$ with cell parameters a=13.5920(8)Å, b=7.4310(5)Å, c=19.6210(1)Å, β=114.554(6)°, V=1802.6(2)Å^3 and Z=4. The structure exhibited intermolecular interaction of the type C-H...O, molecular docking analysis of the title compound is executed with anti-cancerous target with hER-α protein shown high binding affinity. In addition to this Hirshfeld surface computational analysis were carried out. The major inter-contacts contributing to the Hirshfeld surface are H...H, H...Cl, H...C and H...O.

Graphical Abstract



Keywords: Benzophenone, crystal structure, anticancer, Hirshfeld Surfaces.

INTRODUCTION

Heterocyclic compounds have great importance in the field of pharmaceutical industry, among heterocycles benzoimidazole occupied most significant place due to its diverse biological activities. It is a unique heterocyclic compound containing a benzene ring fused to an imidazole ring. The literature survey shows that benzoimidazole possess biological activities such as antimicrobial [1] anti-tuberculosis [2], anti-ulcer [3] and anti-allergic [4] etc. The benzophenone also an important organic compound used as a building block of many pharmaceutical compounds due to its various biological activities such as anti-inflammatory and anticancer etc. [5], hence in the present compound benzophenone is fused to benzoimidazoles to enhance its biological activities, subsequently we performed molecular docking for anti-cancer target with hER-α protein and reported as better binding energy than previously reported ones, hence we report Structural, molecular docking, Hirshfeld surfaces and computational studies of (2-((1H-benzo[d]imidazol-2-yl)methoxy)-5-chlorophenyl)(4-chlorophenyl)Methanone (Fig 1).

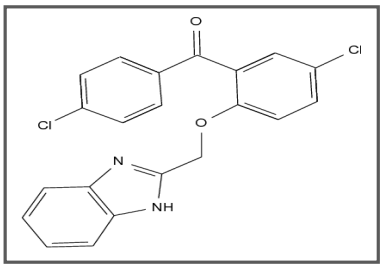


Figure 1. Schematic diagram of the compound.

MATERIALS AND METHODS

A single crystal of the title compound with dimensions 0.30 × 0.27 × 0.25 mm was chosen for an X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3kW sealed X-ray source (graphite monochromated MoK_{α}). The crystal to detector distance is fixed at 120 mm with a detector area of 441 × 240 mm^2 . Thirty six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400s. Successive frames were scanned in steps of 5° per min with an oscillation range of 5°. Image processing and data reduction were done using Denzo [6]. The reflections were merged with Scale pack. All of the frames could be indexed using a primitive monoclinic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97. All of the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [7] with isotropic temperature factors for all the non-hydrogen atoms converged the residuals to 0.1946. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. The residuals finally converged to anisotropic refinement of non-hydrogen atoms was started at 0.0464. The highest peak and the deepest hole in the final difference map were 0.469 and -0.480 e.$Å^{-3}$ respectively. The details of crystal data and refinement are given in table 1.

RESULTS AND DISCUSSION

The bond lengths and bond angles of all the non-hydrogen atoms are given in table 2 which are in good agreement with the standard values [8-9]. ORTEP of the molecule is shown in figure 2. The dihedral angle between the two phenyl rings bridged by the keto-carbonyl group is 67.06(1)° which is significantly very high when compared to the corresponding value of 61.97(12)° reported earlier [10]

The dihedral angle between the benzimidazole ring and phenyl ring makes an angle of 73.37(12)° bridged by the central phenyl ring. The benzimidazole moiety is planar to the phenyl ring as indicated

Table 1. Crystal data and structure refinement details

CCDC Number	CCDC-719540
Empirical formula	$C_{21}H_{14}N_2O_2Cl_2$
Formula weight	397.24
Temperature	293(2)K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_{1/c}$
Cell dimensions	a=13.5920(8)Å, b=7.4310(5)Å, c=19.6210(1)Å, β=114.554(6)°
Volume	1802.6(2) $Å^3$
Density(calculated), Z	1.464 Mg m^{3-1}, 4
Absorption coefficient	0.380 mm^{-1}
F_{000}	816
Crystal size	0.30 × 0.27 × 0.25 mm
Theta range for data collection	2.19^0 to 25.03^0
Index ranges	$-16 \leq h \leq 16$, $-8 \leq k \leq 8$, $-22 \leq l \leq 23$
Reflections collected	5152
Independent reflections	3116
Refinement Method	Full matrix least squares method based on F^2
R_{int}	0.0217
Data / restraints / parameters	3116 / 0 / 246
Goodness of fit of F^2	1.093
Final R indices *[I > 2σ(I)]*	$R_1 = 0.0464$, $wR_2 = 0.1355$
R indices (all data)	$R_1 = 0.0563$, $wR_2 = 0.1548$
Extinction coefficient	0.042(7)
Largest diff. peak and hole	0.469 and -0.480 e. $Å^{-3}$

by the dihedral angle between them is 0.63(1)°. Another indication of the conformation is the values of torsion angles C15-C10-C8-O9=-30.2(3)° and C4-C3-C8-O9=-40.5(3)°. For benzophenones these torsion angles take the same sign and are each reported to be 30° in the energy minimized benzophenone [11]. In benzimidazole moiety, C19-N27 bond of 1.370° is formally treated as a double bond but N20-C19 = 1.301(3)° is shortened comparing to the single C-N (1.47Å) bond. The C19-N27 bond is longer than C19-N20. This shortening of distance is due to electron delocalization in the ring. The C18-O17 bond is in an *-anti-periplanar* conformation, as indicated by the torsion angle value of -74.63(18)° for the atoms C19-C18-O17-C2. The structure is exhibited intermolecular hydrogen bond of the type C22-H22…O9 between benzimidazole ring and the keto-carbonyl group and spread as two dimensional frame works along 'b' axis is shown in figure 3. Whose geometric parameters are depicted in table 3.

Table 2. Selected bond lengths (Å) and bond angles (°)

Bond lengths (Å)				Bond angles (°)			
Atoms	**Bond length**	**Atoms**	**Bond length**	**Atoms**	**Bond angle**	**Atoms**	**Bond angle**
C8-O9	1.217(3)	O17-C18	1.418(3)	C6-C1-C2	119.8(2)	C19-N27-C26	106.26(2)
C8-C10	1.491(3)	C13-Cl16	1.735(2)	O17-C2-C1	123.7(2)	N27-C26-C25	132.9(2)
C2-O17	1.363(3)	C19-N20	1.301(3)	O17-C2-C3	116.26(2)	N27-C26-C21	105.1(2)
C11-C12	1.382(3)	C19-N27	1.370(3)	O9-C8-C3	119.3(2)	C2-O17-C18	118.86(2)
C26-N27	1.386(3)	N20-C21	1.382(3)	C10-C8-C3	120.30(2)	O17-C18-C19	107.72(2)
-	-	-	-	N27-C19-C18	122.6(2)	N20-C19-N27	113.3(2)
-	-	-	-	C19-N20-C21	105.42(2)	N20-C19-C18	124.1(2)
-	-	-	-	N20-C21-C22	129.6(2)	N20-C21-C26	109.9(2)

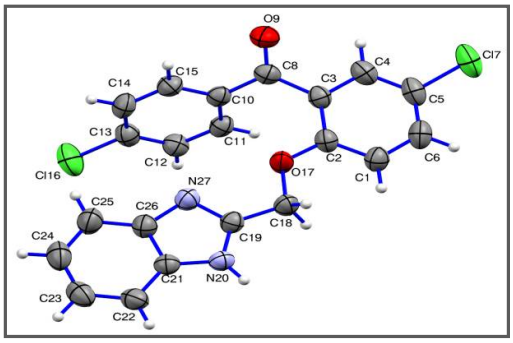


Figure 2. ORTEP diagram of the titled compound drawn at 50% of probability level.

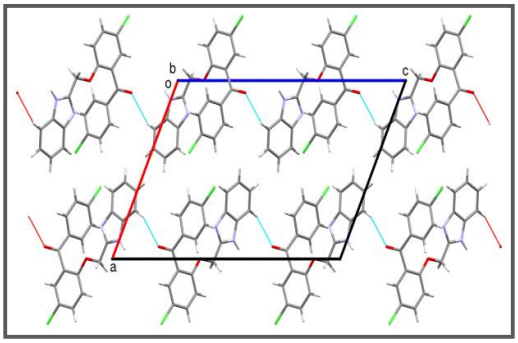


Figure 3. Packing of the molecules when viewed along 'b' axis.

Table 3. Geometric parameters of the intermolecular interactions (Å,°)

D-H...A	D-H	H….A	D…A	Angle	Symmetry code
C22-H22...O9	0.93	2.59	3.413(3)	147	*x, 3/2 - y, 1/2 + z.*

Crystal structure of human estrogen receptor (hERα) (PDB ID: 3PNR) obtained from Protein Data Bank [12]. Three dimensional (3D) structures of the compounds were converted from CIF Format to Mol2 format by Marvin Sketch [13]. AutoDock 4.2 Tools [14] used to simulate the binding conformations between the compounds and protein. AutoDock [15] with grid maps of (60×60×60) was applied to explore the binding sites of the target protein. The sites with lowest binding energies were further analyzed using AutoDock 4.2 (Fig. 4). The grid box size set to (60×60×60Å) and a grid spacing of 0.375 Angstrom. Center of the grid box is set to the center of the protein. Number of GA Runs was 250. Population size was set to 150 with 2,500,000 energy evaluations (medium) and conformational searching was done using the Lamarckian genetic algorithm (LGA). The lowest energy conformation was used for further analysis. According to the Autodock result (Table 4), it can be inferred that the titled compound binding to the target protein and may exhibit anti-cancerous activity with binding energy of -11.6 kcal mol^{-1}, which is relatively larger than binding affinities (-8.2 kcal mol^{-1} and -10.46 kcal mol^{-1}) of other compounds reported earlier for same activity, therefore the titled compound may show better anti-cancerous activity [16-17].

Presence of intermolecular interactions were analyzed using Hirshfeld surface analysis is carried out using Crystal Explorer, 3D Hirshfeld surface is made transparent to visualize arrangement of atoms in the molecule. The 2D fingerprint plots depicts type of intermolecular contacts present in the molecule, and also relative contribution from each type of intermolecular interaction present in the molecule towards the packing of Hirshfeld surface area and it is illustrated in the figure 5 (i-x). Further 2D finger plots revealed major contribution to the packing of molecule are (i) H...H-(36.3%), (ii) H...Cl-(15.9%), (iii) H...C-(13.9%), (iv) H...O- (8.2%), (v) C...C-(7.3%), (vi) C...Cl-(5.9%), (vii) H…N-(5%) is shown in the form of spikes, while that of minor contribution also shown in (viii) Cl...Cl-(3.5%), (ix) C...O-(2.0%), (x) C...N-(0.4%), figure 5(xi) indicates full. The (Fig. 6) percentage of each pair of contact is illustrated in pie chart.

Table 4. Binding Energy of compounds with hER-α protein

Target	Binding Energy in (kcal mol^{-1})
Anti-cancer	-11.6

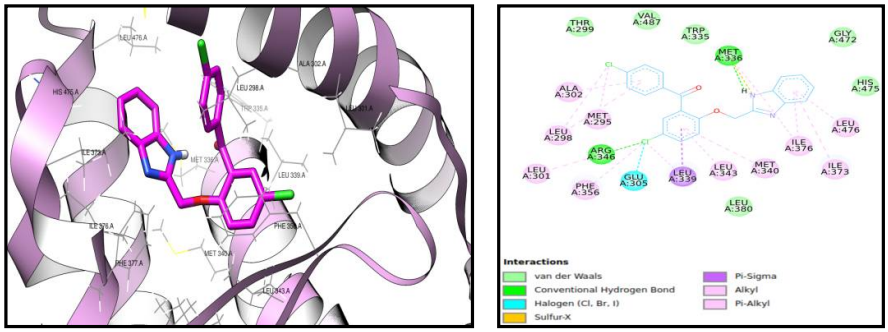
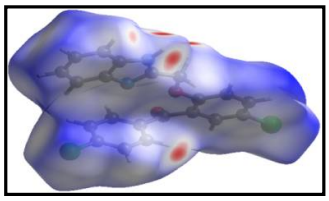
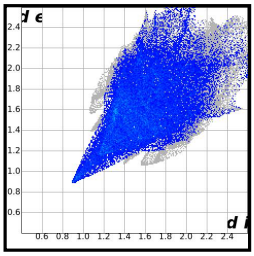


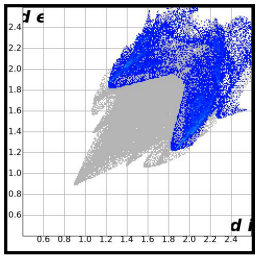
Figure 4. Molecular docking of the compound.



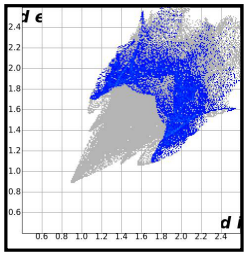
(a)



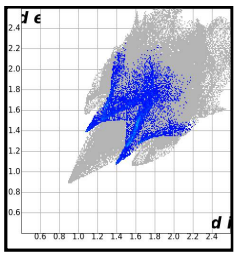
(i) H….H-(36.3%)



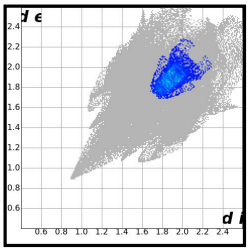
(ii) H…Cl-(15.9%)



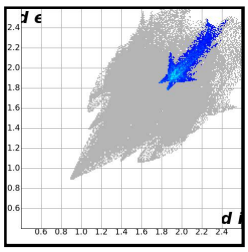
(iii) C…H-(13.9%)



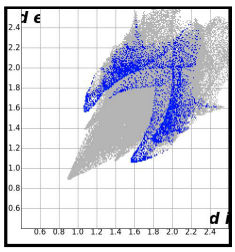
(iv) H…O-(8.2%)



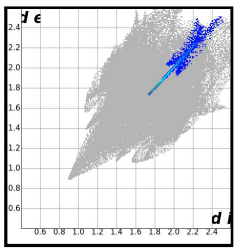
(v) C…C-(7.3%)



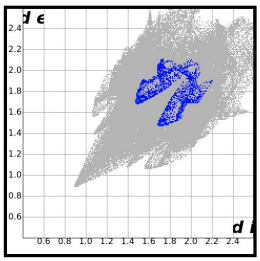
(vi) C…Cl-(5.9%)



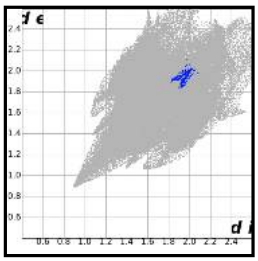
(vii) H…N-(5%)



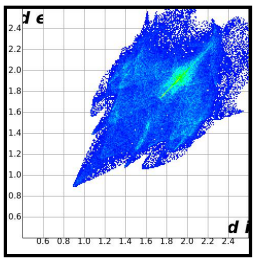
(viii) Cl…Cl-(3.5%)



(ix) C…O-(2.0%)



(x) C…N-(0.4%)



(xi) All

Figure 5. Hirshfeld surface analysis: (a) d_{norm} mapped on Hirshfeld surface for visualizing the inter contacts of the title compound. (b) 2D fingerprint plots (i-x). The outline of the full fingerprint is shown in gray. di is the closest internal distance from a given point on the Hirshfeld surface and de is the closest external contacts.

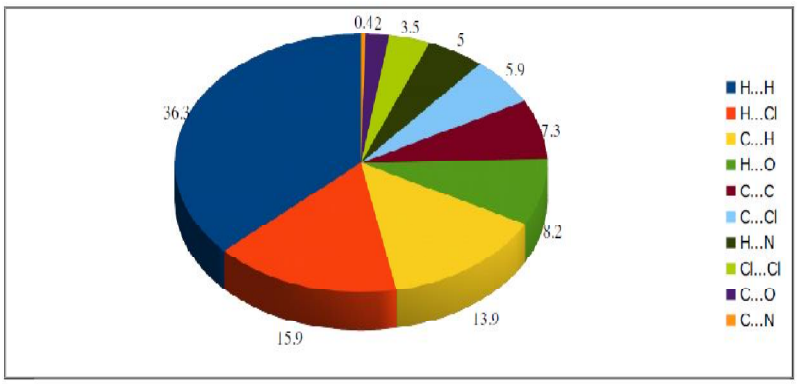


Figure 6. Visualization of percentage of each pair of contacts.

APPLICATION

The precise measurement of atomic positions, bond lengths, bond angles in a molecule and also the compound exhibited high binding affinity for anti-cancer activity.

CONCLUSIONS

The compound is crystallized into monoclinic system with the space group of $P2_{i/c}$. The structure is stabilized with an intermolecular hydrogen bond interaction of the type C-H...O. The molecular docking result showed that the compound has good binding affinity with selected anticancer target protein. Further 2D fingerprint plots revealed H...H, H...Cl and H...C are the major contribution in the packing of 3D Hirshfeld surface.

ACKNOWLEDGEMENTS

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