Synthesis, Structural, Molecular Docking and Hirshfeld Surface Analysis of (2-((6-chloropyridin-3-yl)methoxy)-5 bromophenyl) (4-chlorophenyl) methanone

B. N. Lakshminarayana¹, T. N. Mahadeva Prasad², N. R. Sreenatha³, D. P. Ganesha⁴, B. K. Manuprasad⁵ and S. Nagaraju⁶

¹Department of Engineering Physics, Adichunchanagiri Institute of Technology, Chickamagalur - 577102, Karnataka, INDIA.
²Department of Physics, Government First Grade College, Bannur - 571101 Karnataka, INDIA.
³Department of Physics, Government Engineering College, Hassan - 573201, Karnataka, INDIA.
⁴Department of Physics, Rajeev Institute of Technology, Hassan - 573201, Karnataka, INDIA.
⁵Department of Chemistry, Jain College of Engineering, Belagavi - 590014, Karnataka, INDIA.
⁶Department of Physics, Manasa Gangotri, University of Mysore, Mysuru, Karnataka, INDIA.

email: bnlphysics@gmail.com

(Received on: December 14, 2017)

ABSTRACT

The title compound (2-((6-chloropyridin-3-yl)methoxy)-5-bromophenyl) (4-chlorophenyl) methanone was synthesized and characterized by spectroscopically (HRMS, IR and ¹H NMR) single crystal X-ray diffraction studies, molecular docking and Hirshfeld surface analysis. The title compound C₁₉H₁₂NO₂Cl₂Br crystallizes in the monoclinic space group with cell parameters a = 8.4160(8) Å, b = 17.191(3) Å, c = 12.302(2) Å, α = 90°, β = 90.374(3)°, γ = 90°, V = 1774.7(5) Å³ and Z = 4. The pyridine ring and the phenyl ring bridged by the central phenyl ring are nearly coplanar. The docking analysis of the title compound is executed with anti-cancer target with hER-α protein. In addition to this Hirshfeld surface computational analysis was carried out. The major intercontacts contributing to the Hirshfeld surface are H...H, H...Cl, H...C and H...Br.

Keywords: Benzophenone; crystal structure; pyridine ring; anti-inflammatory; anticancer.
1. INTRODUCTION

Functionalized phenols, such as 2-hydroxy benzophenones, represent important building blocks in organic and medicinal chemistry. Benzophenone is a prototypical aromatic carbonyl compound that has been extensively studied. The great importance of these substances is fundamentally due to the diverse biological and chemical properties that they possess. Benzophenones are usually obtained from natural products or by synthetic methods. Benzophenones are frequently used in medicine and industry. The proficiency of benzophenone analogues as chemotherapeutic agent especially as anti-inflammatory is well documented. Benzophenone analogues have been reported to be effective anti-inflammatory agents. Recently synthesis and structure activity relationship of benzophenones as novel class of p38 MAP kinase inhibitors with high anti-inflammatory activity have been reported. The in-vitro and in-vivo studies of novel nitro and amino substituted benzophenones have been investigated as potential anticancer agents with low cytotoxicity. In the light of these observations and our exploration for new molecules with anti-inflammatory activity, encouraged us to integrate 2-chloro-5-chloromethyl pyridine moiety in benzophenone framework, since these systems possess well documented anti-inflammatory activity and anticancer activity.

2. PROCEDURE

2.1 Synthesis and crystallization

4-Chloro-benzoic acid 4-bromo-phenyl ester (3) was synthesized by benzylation of 4-bromo-phenol (1) with 4-chloro benzoyl chloride (2) using 10% sodium hydroxide solution. (5-bromo-2-hydroxy-phenyl)-(4-chloro-phenyl)-methanone (4) was synthesized by Fries rearrangement of the above ester in the presence of anhydrous aluminium chloride. A mixture of 4 (1g, 4.41 mM) and 2-chloro-5-chloromethyl pyridine (0.95 g, 4.41 mM) was refluxed in dry acetonitrile for 5h, in the presence of anhydrous potassium carbonate (1.83 g, 13.25 mM). When the reaction was completed (TLC), the reaction mass was cooled and the solvent was removed under reduced pressure. The residual mass was triturated with ice cold water to remove potassium carbonate and then extracted with dichloromethane (3× 20 ml). The organic layer was washed with 10% sodium hydroxide solution (3×10 ml) followed with water wash (3×15 ml) and then dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to obtain the crude solid, which upon recrystallization with ethanol afforded (2-((6-chloropyridin-3-yl) methoxy)-5-bromophenyl) (4-chlorophenyl) methanone (5) as pale yellow crystals, in good yield (Scheme 1).
2.2 Single crystal X-ray Diffraction

Single crystals of suitable size were chosen for X-ray diffraction studies. The data were collected at room temperature on a DIPlabo Image Plate system with graphite monochromated radiation MoKα. Each exposure of the image plate was set to a period of 400s. Thirty-six frames of data were collected in the oscillation mode with an oscillation range of 5° and processed using Denzo. The reflections were merged with Scalepack. All the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods using SHELXS. Least squares refinement using SHELXL with isotropic temperature factors for all the non-hydrogen atoms converged the residual to 0.1993. Subsequent refinements were carried out with anisotropic temperature factors for the hydrogen atoms. The hydrogen atoms were allowed to ride on their parent atoms. The residual finally converged to 0.0453.

2.3 Molecular Docking

Crystal structure of human estrogen receptor (hERα) (PDB ID:3PNR) obtained from Protein Data Bank. Three dimensional (3D) structure of the compounds were converted from CIF Format to Mol2 format by MarvinSketch. AutoDock 4.2 Tools used to simulate the
binding conformations between the compounds and protein. AutoDock\textsuperscript{32} 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. The grid box size set to (60×60×60Å) and a grid spacing of 0.375 Angstrom. Center of the grid box 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.

3. RESULTS AND DISCUSSIONS

3.1 Spectral data of compound (2-((6-chloropyridin-3-yl)methoxy)-5 romophenyl) (4-chlorophenyl) methanone

Yield 1.40 g(88 %): M.p. 174°C; IR (Nujol): 1716 cm\(^{-1}\) (C=O); \(^1\)NMR (CDCl\(_3\)) δ 4.90 (s, 2H, CH\(_2\)), 6.74-8.71 ppm (m, 10H, J=7 Hz, Ar-H). Anal. Calcd. For C\textsubscript{19}H\textsubscript{12}BrCl\textsubscript{2}NO\textsubscript{2}: C, 52.21; H, 2.77; N, 3.20. Found: C, 52.20; H, 2.74; N, 3.18%.

3.2 Molecular and crystal structure

![Figure 2. The ORTEP diagram of the ligand showing 50% probability displacement ellipsoids.](image)

The details of crystal data and refinement are given in Table 1. Figure 2 represents the ORTEP\textsuperscript{33} diagram of the molecule with thermal ellipsoids drawn at 50% probability. The bond lengths and bond angles are in good agreement with those reported compounds\textsuperscript{34}. In the title compound (2-((6-chloropyridin-3-yl)methoxy)-5-bromophenyl)(4-chlorophenyl) methanone, the dihedral angle between the two phenyl rings bridged by the keto carbonyl group is 71.31(2)° is less compared to the other reported compounds\textsuperscript{34} and high as compared with other reported compounds\textsuperscript{34}. The pyridine ring and the phenyl ring bridged by the central phenyl
ring (C1-C2-C3-C4-C5-C6) are nearly coplanar, as indicated by the dihedral angle of 4.6(2)°. The dihedral angle between the pyridine ring and the central phenyl ring is 69.1(2)°. Another indication of the conformation is the values of the torsion angles C1-C2-C17-O18 = -33.7(6)° and C20-C19-C17-O18 = -45.1(7)°. For benzophenones these torsion angles take the same sign and are reported to be 30° in the energy minimized benzophenone35. The C9-O8 bond is in an -anti-periplanar conformation, as indicated by the torsion angle value of -160.7(4)° for C10-C9-O8-C3. The packing of the molecule when viewed long the ‘a’ axis is shown in the Figure 3. No classical hydrogen bonds are observed.

![Figure 3. The packing of the compound along ‘a’ axis.](image)

### 3.3 Molecular docking

![Figure 4. Molecular docking of the Compound 2-((6-chloropyridin-3-yl)methoxy)-5 bromophenyl) (4-chlorophenyl) methanone.](image)

According to the Autodock Vina result (Table 4), it can be inferred that the compound (2-((6-chloropyridin-3-yl)methoxy)-5bromophenyl)(4-chlorophenyl)methanone is binding to protein (hERα)(PDB ID:3PNR) as shown in the Fig. 4. The binding affinity value of -10.46 kcal/mol shows lowest binding affinity towards the protein estrogen with those of the earlier
Based on the molecular docking studies we found that ligand hERα has the potential for application as inhibitor for breast cancer cell.

### 3.4 Hirshfeld surface analysis

Presence of intermolecular interactions are 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 summarizes type of intermolecular contacts present in the molecule, and also relative contribution from each type of interaction present in the molecule to the packing of Hirshfeld surface area and it is illustrated in the Figure 5 (a-j). Further 2D finger plots reveals major contribution to the packing of molecule (a) H...H-(21.1%), (b) H...Cl-(18.1%), (c) H...C-(16.9%), (d) H...Br-(10.9%), (e) H...O-(9.1%), (f) H...N-(5.9%) is shown in the form of spikes, while that of minor contribution also shown (g) C...Cl-(3.9%), (h) C...Br-(3.1%), (i) C...C-(2.9%).

![Hirshfeld surfaces analysis](image)

**Figure 5.** Hirshfeld surfaces analysis: (a) d_{norm} mapped on Hirshfeld surface for visualizing the inter contacts of the title compound. (b) Fingerprint plots- (a)-(j). The outline of the full fingerprint is shown in gray. d\textsubscript{i} is the closest internal distance from a given point on the Hirshfeld surface and d\textsubscript{e} is the closest external contacts.
Table 1. Crystal Data and Structure Refinement details for the title compound.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCDC Deposition Number</td>
<td>CCDC-719331</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{19}H_{12}NO_{2}Cl_{2}Br</td>
</tr>
<tr>
<td>Formula weight</td>
<td>437.11</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Cell dimensions</td>
<td>a = 8.4160(8) Å, b = 17.191(3) Å, c = 12.302(2) Å, β = 94.374(3)°</td>
</tr>
<tr>
<td>Volume</td>
<td>1774.7(5) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density(calculated)</td>
<td>1.636 mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>2.630 m/m</td>
</tr>
<tr>
<td>F(000)</td>
<td>872</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.3 × 0.27 × 0.25 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.04° to 25.03°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>−9 ≤ h ≤ 8, −20 ≤ k ≤ 20, −14 ≤ l ≤ 14</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>5130</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2823</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Empirical (SHELXA)</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2823 / 0 / 227</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.019</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ(I)]</td>
<td>R₁ = 0.0442, wR₂ = 0.1162</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.347 and -0.665 e.Å</td>
</tr>
</tbody>
</table>

Table 2: Binding Energy of compounds with hER-α protein

<table>
<thead>
<tr>
<th>PDB ID</th>
<th>Target</th>
<th>Binding Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3PNR</td>
<td>Anti-cancer</td>
<td>-10.46</td>
</tr>
</tbody>
</table>

CONCLUSION

The compound (2-((6-chloropyridin-3-yl)methoxy)-5-bromophenyl)(4-chlorophenyl) was synthesized and characterized by ¹H NMR, IR and X-ray diffraction studies. The reported

Benzophenone substituted derivatives are used in industry, cosmetics, medicine and agriculture purposes. Benzophenone analogues are used as sunscreen agents. The chlorine substituted benzophenone have been investigated as potential anticancer agents and antiinfectives. The molecular docking results show the binding of the title compound to the selected anticancer target protein with high binding affinity. Further 2D fingerprint plots revealed H...H-(21.1%), H...Cl-(18.1%), H...C-(16.9%), H...Br-(10.9%) are major contribution in the packing of 3D Hirshfeld surface area.

ACKNOWLEDGMENTS

The authors are grateful to DST and Government of India project SP/12/FOO/93, University of Mysore, Mysore for financial assistance and also thankful Devashis Das, DFTR, Bengaluru for molecular docking studies.

REFERENCES

32. Vina, AutoDock. "Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading Trott, Oleg; Olson, Arthur.