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# Synthesis, Spectroscopy, X-Ray Crystallographic Investigation and Molecular Docking of 2-(2-Chloro-Phenyl)-3-(3, 3-Diphenyl-Propyl)-Thiazolidin-4-One

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**ABSTRACT**

The title compound $C_{24}H_{22}ClNOS$, crystallizes in monoclinic space group $P2_1/c$ with Z=8. The crystallographic parameters are a= 10.1508(2) Å, b= 10.6441(2) Å, c= 38.4180(6) and β= 95.9500(10)°. There are two independent molecules per asymmetric unit. The dihedral angles between two phenyl rings are 82.85(7) for molecule 1 and 88.05 (10) for molecule 2. The stability of the structure is due to weak but significant C-H…O, π-π, C-H… π and C-Cl…π interactions. The structure has been refined to a final R = 0.0543 for the 7308 observed reflections with $I \geq 2\sigma$ (I). Protein-ligand interaction plays an important role in structural based drugs design. In our research we have selected different receptor. The receptors were docked with thiazolidine derivative and the energy value obtained.



## Introduction

Thiazolidine derivative is significant member of heterocyclic compound. Many compounds containing thiazolidine group possess a broad spectrum of biological activities [1-2]. Thiazolidine derivatives exhibit herbicidal[3-4], antineoplastic[5], hypolipidemic[6] and anti-inflammatory[7] activities. Thiazolidin-4-one derivatives are known to exhibit diverse bioactivities such as anti-histaminic[8], anti-microbial[9-10a], PAF antagonist[11], cardioprotective[10b], anti HIV[12], and tumor necrosis factor-α antagonist activities[13]. As part of our ongoing research on systematic characterization of novel heterocyclic compounds. We synthesized a novel thiazolidine derivatives, 2-(2-chloro-phenyl)-3-(3,3-diphenyl-propyl)-thiazolidin-4-one (Figure.1).

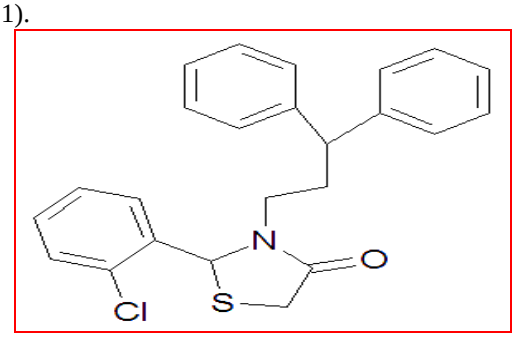


**Figure 1. Chemical Scheme of the Title Compound**

X-ray crystallography of the title compound confirm that there are two independent molecules in the asymmetric unit. Thiazolidine ring of molecule B is puckered where as that of molecule A is planar. Halogen Cl contributes to the stability of molecular packing. Computational Biology and bioinformatics are useful for the drug recovery process which reduces the cost of drugs. Rational Drug Design is the inventive process of finding new medications based on the knowledge of the biological target[14]. Docking of the drug molecule with the receptor is one of the methods to identify novel compounds. The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor [15].

## Experimental

### Preparation of 2-(2-chloro-phenyl)-3-(3, 3-diphenyl-propyl)-thiazolidin-4-one

A mixture of 3,3-diphenyl propylamine ( 0.01 mol) and 2-Chloro benzaldehyde ( 0.01 mol) in dry toluene (50 ml) is refluxed until no more water is collected in a Dean–Stark water separator. The reaction is simultaneously monitored by TLC. To this crude mixture, mercaptoacetic acid (0.01mol) is added dropwise and the reaction mixture is heated at reflux temperature for 10-15 h. The reaction mixture is cooled to room temperature and evaporated to dryness under vacuo. The crude compound obtained is taken up in chloroform (200 mL). The organic layer is washed with 5% aq. citric acid (100mL), followed by water (200 mL), 5% aq. Sodium hydrogen carbonate (100 mL) and brine (100 mL). The organic layer is dried over anhydrous sodium sulphate and the solvent is removed under reduced pressure. The crude product obtained is purified by column chromatography (SiO2) using hexane–ethyl acetate (8:2) as an eluent. The fraction containing main products are combined and evaporated to dryness under reduce pressure. The residue is crystallizes from ethanol to give pure product.

### X-Ray Crystallography

Single crystal of the title compound is obtained by slow evaporation in Methanol. X-ray data collection for 2-(2-chloro-phenyl)-3-(3,3-diphenyl-propyl)-thiazolidin-4-one is performed at room temperature [298(2) K] on a Kappa Apex II CCD Diffractometer[16] using graphite monochromated Mo $K_\alpha$ radiation (0.7107 Å) in the ω–2θ scan mode in θ range 1.07 - 27.58. Relevant crystallographic data are shown in Table 1. The structure is solved by direct methods locating most non-hydrogen atoms with SHELXS-97[17].The Structure is refined by full matrix least squares on $F^2$ with SHELXL-97[18]. Programs SHELXL-97 and ORTEP-3[19] built in WinGX [20] programme used to prepare materials for publications. All hydrogen atoms are calculated at idealized positions, with fixed distances (0.93Å for C (aromatic)–H, 0.96Å for C (primary)–H and 0.86Å for N (primary)–H) and refined with isotropic displacement

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parameters related to the equivalent isotropic displacement parameter of the atom to which it is bonded. ORTEP view of the 2-(2-chloro-phenyl)-3-(3,3-diphenyl-propyl)-thiazolidin-4-one shows the atoms labeling and the 30% probability ellipsoids. (Figure 2).

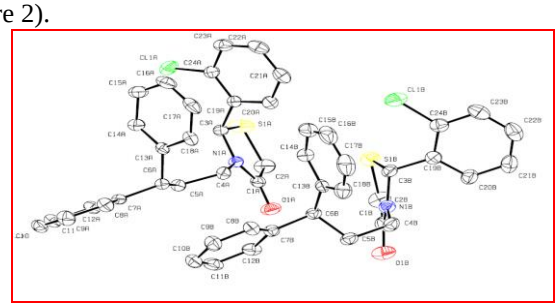

**Figure 2. ORTEP view of the title compound showing the atoms labeling and the 30% probability ellipsoids**

**Molecular Docking Using Hex and Schrodinger**

Computer-Aided Drug Design (CADD) is a specialized discipline for the study of simulation of ligand- receptor interactions and is strongly dependent on bioinformatic tools, applications and databases. The structure of thiazolidine receptors were referred from different journals and retrieved from PDB data bank[21]. Thiazolidine derivatives which have been synthesized by us and three dimensional structures of this derivative have been worked out. The corresponding CIF files of this derivative have been converted into PDB file using OBGUI software [22]. These PDB structures are used for the docking studies using Hex software [23]. The receptor are to be the best inhibitor of the ligand when ligand-receptor docks each other well.

The parameters used for the docking process were

1. Correlation type – Shape only
2. FFT Mode - 3D fast lite
3. Grid Dimension - 0.6
4. Receptor range – 180
5. Ligand range – 180
6. Twist range – 360
7. Distance Range – 40

The title compound is docked with the receptors using the above parameters.

**Results**

The compound crystallizes in monoclinic space group $P2_1/c$ with Z=8. The crystallographic data are presented in Table 1. The selected bond distances and bond angles are listed in Table 2 Docking results between the 2-(2-chloro-phenyl)-3-(3,3-diphenyl-propyl)-thiazolidin-4-one and few selected receptor (using HEX) are tabulated in Table 3.

**Discussion**

The asymmetric unit of the title compound consists of two independent molecules (A and B). Bond lengths and angles are in the normal range and very well comparable to similar structure.[25] In the molecules, the thiazolidine ring forms dihedral angles of 69.30 (7)° and 72.67 (6) ° with Chloro benzene ring. The bond length of five member ring varies from 1.343 (3) Å to 1.834 (2) Å and 1.345 (3) Å to 1.832 (2) Å for molecule A and B respectively. Bond angles of five membered ring varies from 94.1 (1)° to 119.5 (2)° and 92.3 (1)° to 118.6 (2) for molecule A and B respectively. The torsional angles of molecule A C3A-N1A-C4A-C5A, C2A-S1A-C3A-N1A, C4A-N1A-C3A-S1A and C4A-C5A-C6A-C7A are 75.0(2)º, 4.1(2)º, -178.0(1)º and -173.0(2)º respectively and those of molecule B C3B-N1B-C4B-C5B, C2B-S1B-C3B-N1B, C4B-N1B-C3B-S1B, and C4B-C5B-C6B-C7B are 107.4(2), -19.8(2), -166.1(2) and 171.9(2) respectively. The crystal structure is stabilized by inter molecular C-H…O hydrogen bonding interactions (Table 4).

Halogen 'Cl' contribute very actively in stability of the structure which forms intra C-H···Cl and inter C- Cl···π interactions in supramolecular aggregation. Halogen chlorine of the screw related molecule [x,y,z] works as acceptor via C3A – H3A ···Cl1B. The supramolecular structure further supported by π-π interaction. Thiazolidine ring centroid interact with halogen Cl1A which forms C24A—Cl1A···π interaction [Cl1A···Cg1 (1-X,-Y,-Z) = 3.507 Å, where Cg1 is the centroid of the thiazolidine ring (S1A/N1A/C1A/C2A/C3A) (Figure 3).

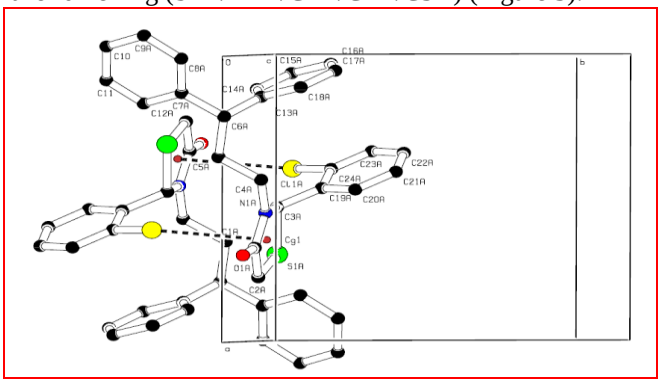

**Figure 3. C- Cl···π interaction in the title compound**

A π-π interaction is observed between the two symmetry related phenyl rings [Cg4···Cg4 (1-X, 1-Y,-Z) = 3.697Å, where Cg4 is the centroid of the C19A—C24A phenyl ring of molecule A. Phenyl ring centroid interact with C2A via hydrogen H2A which forms C2A—H2A···π interaction [H2A···Cg3 (-1+X, Y, Z) = 2.71 Å, where Cg3 is the centroids of the phenyl ring (C13A-C18A) of molecule A. The packing diagram of the molecule is shown in Figure 4.

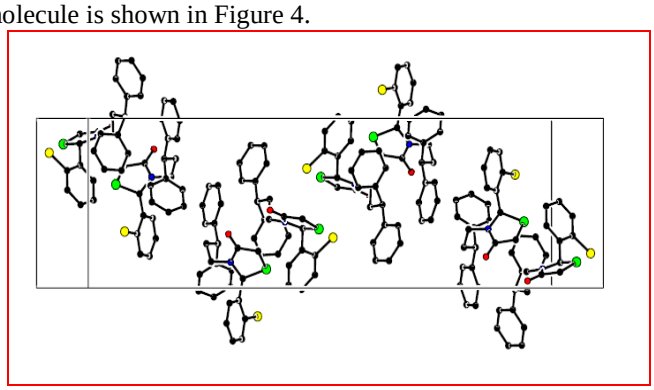

**Figure 4. Packing diagram of the title compound**

The thiazolidine ring of molecule B is puckered [Cremer & Pople Puckering Parameters: puckering amplitude (Q) = 0.246(2) Å, Φ = 174.0(6) º].[26] The Pseudo rotation Parameters P and Tau (M) are P = 332.0(4) º, Tau (M) = 21.7(1) º for S1B - C2B bond[27] whereas that of molecule A is planar. Docking studies are the presently promising tool towards the drug development in present scenerio.

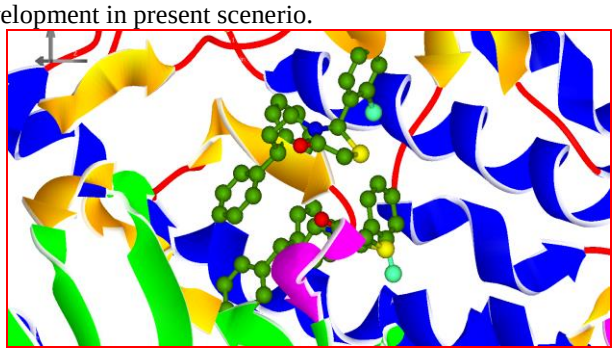

**Figure 5. Interaction of title molecule with 2VOD receptor**

**Table 1. The Crystallographic Parameters with its Standard Deviation of the Title Compound**

| **CCDC No** | **968823** |
|---|---|
| Empirical formula | $C_{24}H_{22}$ Cl N O S |
| Formula weight | 407.94 |
| Temperature (K) | 293 K |
| Wavelength (Å) | 0.71073 |
| Crystal system, Space group | Monoclinic, $P2_1/c$ |
| a (Å) | 10.1508(2) |
| b (Å) | 10.6441(2) |
| c (Å) | 38.4180(6) |
| α (°) | 90.00 (0) |
| β (°) | 95.9500(10) |
| γ (°) | 90.00 (0) |
| Volume ($Å^3$) | 4128.55(13) |
| Z | 8 |
| Calculated density (Mg $m^{-3}$), | 1.309 |
| Absorption coefficient ($mm^{-1}$) | 0.301 |
| F(000) | 1704 |
| θ range for data collection (°) | 1.07 - 27.58 |
| Limiting indices | $-13 \leq h \leq 10$ ; $-12 \leq k \leq 13$; $-49 \leq l \leq 49$ |
| Reflections collected/unique | 9485/ 7308 |
| Absorption correction | N.A. |
| Refinement method | Full Matrix Least Square of $\|F\|^2$ |
| Data/restrains/parameters | 9485/0/ 505 |
| Goodness-of-fit on $F^2$ | 1.082 |
| Final R indices | $R_1 = 0.0543$, $wR_2 = 0.1523$ |
| R indices (all data) | $R_1 = 0.0731$, $wR_2 = 0.1738$ |
| Largest diff. peak and hole (e $Å^{-3}$ ) | 0.513 and -0.565 |

**Table 2. Selected bond lengths and bond angles of the title compound**

| **Few selected Bond Length (Å)** | | | |
|---|---|---|---|
| **Molecule A** | | **Molecule B** | |
| Cl1A - C24A | 1.740(2) | Cl1B - C24B | 1.737(3) |
| S1A -C2A | 1.784(3) | S1B -C2B | 1.796(3) |
| O1A -C1A | 1.216(3) | O1B -C1B | 1.220(4) |
| S1A -C3A | 1.834(2) | S1B -C3B | 1.832(2) |
| N1A -C1A | 1.344(3) | N1B -C1B | 1.344(3) |
| N1A -C4A | 1.460(2) | N1B -C4B | 1.465(3) |
| C3A -C19A | 1.511(3) | C3B -C19B | 1.513(3) |
| C4A -C5A | 1.521(3) | C4B -C5B | 1.525(4) |
| C5A -C6A | 1.536(3) | C5B -C6B | 1.533(3) |
| C6A -C7A | 1.516(3) | C6B -C7B | 1.531(3) |
| C6A -C13A | 1.521(3) | C6B -C13B | 1.510(3) |
| Few selected Bond Angles (º) | | | |
| Molecule A | | Molecule B | |
| C2A - S1A - C3A | 94.10(10) | C2B - S1B - C3B | 92.30(12) |
| C1A - N1A - C3A | 119.55(17) | C1B - N1B - C3B | 118.6(2) |
| O1A - C1A - N1A | 124.6(2) | O1B - C1B - N1B | 124.3(2) |
| S1A - C3A - N1A | 105.36(13) | S1B - C3B - N1B | 104.86(14) |
| C4A - C5A - C6A | 110.45(17) | C4B - C5B - C6B | 114.2(2) |
| N1A - C3A - C19A | 113.88(17) | N1B - C3B -C19B | 113.59(19) |
| C19A - C24A - Cl1A | 119.72(18) | C19B - C24B - Cl1B | 119.3(2) |
| C13A - C6A - C5A | 109.73(16) | C13B - C6B - C5B | 114.9(2) |
| C19A - C3A - S1A | 110.18(14) | C19B - C3B - S1B | 112.38(16) |

**Table 3. Docking results of title compound and different receptors**

| **2-(2-chloro-phenyl)-3-(3,3-diphenyl-propyl)-thiazolidin-4-one** | | | | | |
|---|---|---|---|---|---|
| Receptors | 2UZL | 2UZN | 2UZO | 2VOD | 4ENY |
| E - Value | -267.97 | -60.5 | -342.02 | -342.4 | -341.0 |

**Table 4. Hydrogen bond interaction in the title compound**

| **Donor -H....Acceptor** | **D - H** | **H...A** | **D...A** | **D - H...A** |
|---|---|---|---|---|
| C23B-H23B...O1A (i) | 0.93 | 2.54 | 3.402(4) | 154 |

**Conclusion**

The title compound synthesized and very well characterized. The title compound further characterized by single crystal X-ray diffraction and its three dimensional structures is work out. From the docking studies it is clear that HUMAN CDK2 protein treated with ligand showing good pose result. Among the five (2UZL, 2UZN, 2UZO, 2VOD, 4ENY) 2VOD is found to be more suitable target receptor (Figure 5). This interaction of ligand with receptor plays a significant role in structure based drug designing. The result shows that four proteins ligand interactions are good and have agreeable values.

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