Crystal Structure and Docking Studies of (E)-2-(4-(dimethylamino) benzylidene) hydrazinecarbothioamie

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Abstract: ***The Schiff based compound (E)-2-(4-(dimethylamino) benzylidene) hydrazinecarbothioamide (DBHC) crystallizes in monoclinic crystal system, $P2_1/c$ space group. The benzylidene ring is planar conformation with the maximum deviation of atom C(11) is 0.008(3)Å. The crystal packing is stabilized by N-H…S and N-H…N type of intra and inter-molecular interactions. N3 (x, y, z) atom donate proton to acceptor S1 atom (1+x,y,z) which form a $R^2_2(8)$ dimer, these connected the molecules running along a-axis. The title compound is well docked with the protein compared to the co-crystal ligand.***

Keywords: Crystallography, Refinement, Molecular Docking, Glide.

1. Introduction

Metal complexes based on Schiff bases have attracted much attention because of their biological activity [5]. Many Schiff base derivatives have been synthesized and employed to develop protein and enzyme mimics [7], such as models to mimic hydrolase in the hydrolysis of p-nitrophenyl picolinate.

Structural investigations provide useful information on the coordination properties of Schiff bases functioning as ligands. Over the past thirty years, extensive chemistry has surrounded the use of Schiff base ligands in inorganic chemistry. Consequently, a large number of these species have been reported to be superior reagents in biological, pharmacological, clinical and analytical applications [10]. As part of an investigation of their crystal structures, which will provide useful information for the coordination properties of Schiff bases functioning as ligands, we report here the synthesis and molecular structure of the title compound.

In the present study, we report the synthesis and molecular structure of a (E)-2-(4-(dimethylamino) benzylidene) hydrazinecarbothioamide (DBHC). It is a Schiff base derivative and its schematic diagram is shown in figure1.

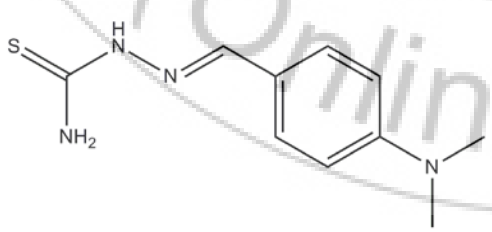


Figure 1: Schematic diagram of Schiff based compound DBHC

2. Methodology

2.1 X-ray Crystallography

X-ray crystallography is a tool used to determine the three-dimensional structure of molecules. The structural and conformational studies of molecules become essential to understand their function. The crystallographic studies not only provide knowledge about the conformation but also about the factors that keep the molecules in the desired conformation. The conformation of biomolecules plays a major role in the design of drugs.

The process of crystallization is one of the ordering, wherein randomly arranged ions, atoms or molecules take up regular positions in the solid state. It involves the phenomenon of nucleation and it may be considered to be in dynamic equilibrium between particles in the fluid phase and solid phase from saturated solutions. Several techniques are available for crystallization of small molecules suchas slow evaporation, slow cooling, diffusion methods etc.

X-ray diffraction is the most powerful technique used to determine the three-dimensional structure of molecules. In the present study, reflection data for the crystal was measured by Bruker Kappa APEX-2 CCD Diffractometer [2]. The raw data collected from the diffractometer suffers from physical and geometrical error factors and hence cannot be used for structure elucidation straight away. Therefore the intensity data have to be corrected for Lorentz, polarization andabsorption effects. The space group of the crystal is determined from the systematic absences of the reflections and by intensity statistics.

2.2 Structure Solution and Refinement

The structure solution can be obtained by any one of the methods that determine the correct phases without any ambiguities. Here we used direct methods for structure solution in which the phases are directly obtained from the

observed intensities. The computer program SHELXS97 is used for the structure solution [8].

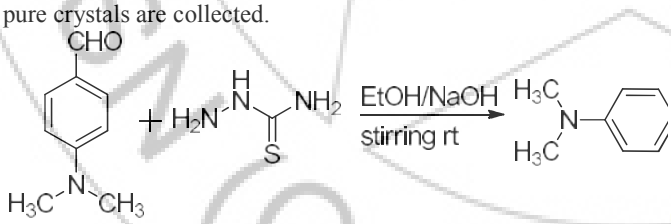
Structure refinement consists of obtaining the best fit between a set of observed measurements and the quantities calculated from a model postulated to explain them. Differences between the observed and the calculated values can arise due to random errors (statistical fluctuations) in the observations and defects in the model (systematic errors). The trial structure obtained from the structure solution is refined in order to get the accurate atomic positions and the associated thermal parameters. Though several structure refinement process are in vogue, the full-matrix least-squares refinement technique is the conventional one and more widely used in small molecular structure determination. The computer program SHELXL97 is used for the refinement [8].

2.3 Molecular Docking

Docking is the best way to put two molecules together. In docking, three steps are to be followed. i) Definition of the structure of the target molecule. ii) Location of the binding site and iii) Determination of the binding mode. By docking, we can identify the perfect or efficient drugs of diseases. We can able to generate different conformations for the ligand (or drug) with their target, so that the drug is to be identified as robust or not. If the binding affinity of the ligand is more for the target, then that will be the potent drug. Determination of the structure of a receptor-ligand complex is a prerequisite for estimating the binding affinity or binding free energy between the molecules. The program GLIDE was used for molecular docking.

2.4 Synthesis

A mixture of 4-(dimethylamino)benzaldehyde with 4-methyl benzylamine and Sodium hydroxide as a catalyst at room temperature is stirred for 30 minutes. The mixture was poured into crushed ice and the resulting yellow precipitate is filtered, the crude product recrystalized from ethanol and pure crystals are collected.



2.5 Data Collection and Structure Refinement

Crystal X-ray diffraction is a very powerful and efficient analytical technique. The results obtained from this technique are most reliable and accurate. Single crystals suitable for X-ray diffraction were successfully grown for DBHC compound. X-ray diffraction was carried out using Bruker Kappa APEX-2 CCD Diffractometer [2]. Cell refinement and data reduction was done using *SAINT [2]*. Program *SHELXS97 [8]* was used to solve structure. To refine structure *SHELXL97[8]* was employed. All molecular graphics were generated using softwares *PLATON, MERCURY* and *DIAMOND* [9].

3. Results and Discussion

3.1 Structural Analysis

The crystal data and refinement parameters for DBHC are given in Table.1. The title compound crystallizes in monoclinic crystal system, $P2_1/c$ space group. The *ORTEP* plot of DBHC is given in Figure 2 [4].

Table 1: Crystallographic Parameters

Parameters	Values
Empirical formula	$C_{10}H_{14}N_4S$
Formula weight	222.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 5.6883(8) Å
	b = 8.9470(12) Å β = 107.614(14) °
	c = 23.808(3) Å
Volume	1154.8(3) A^3
Z, Calculated density	4, 1.279 Mg/m^3
Absorption coefficient	0.254 mm^{-1}
F(000)	472
Crystal size	0.25 x 0.28 x 0.30 mm
Theta range for data collection	2.90 to 25.00 °
Limiting indices	-6<=h<=6, -5<=k<=10, -12<=l<=28
Reflections collected / unique	4001 / 2037 [R(int) = 0.0255]
Completeness to theta = 25.00	99.90%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2037 / 0 / 142
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1069
R indices (all data)	R1 = 0.0736, wR2 = 0.1190
Largest diff. peak and	0.178 and -0.163 e.A^{-3}

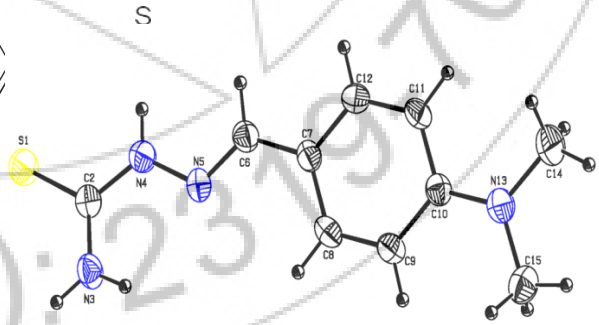


Figure 2: The structure of DBHC, with displacement ellipsoids drawn at the 30% probability level

The structure was solved by direct methods and refined by full-matrix least-squares procedures to a final R-value of 0.048. The benzylidene ring is in planar conformation with the maximum deviation of atom C(11) is 0.008(3)° [3,6]. The dimethylamino-benzylidene group and hydrazinecarbothioamide group are lie in a plane which can

be seen from the dihedral values of 2.64(10)° and also from the torsion angle [N5/C6-C8=] 5.6(4)° [1]. The sum of the bond angles at N13[356°] of the dimethylamino group is in accordance with sp^2 hybridization.

The crystal packing is stabilized by N-H…S and N-H…N type of intra and inter-molecular interactions (Table.2). N3 (x, y, z) atom donate a proton to acceptor S1 atom (1+x,y,z) which form a $R^2_2(8)$ dimer, these connected the molecules running along a-axis as shown in Figure 3.

Table 2: Hydrogen bonding interaction (Å & °)

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3A)...S(1)[i]	0.86	2.84	3.409(2)	125
N(3)-H(3B)...S(1)[ii]	0.86	2.56	3.406(2)	169

Systematic Equivalent positions: i) 1+x,y,z ii) 1-x,-y,1-z

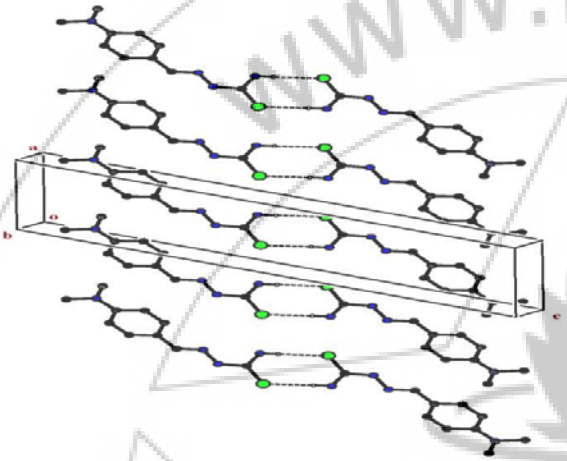


Figure 3: Packing diagram for DBHC with hydrogen bonds drawn as dashed lines.

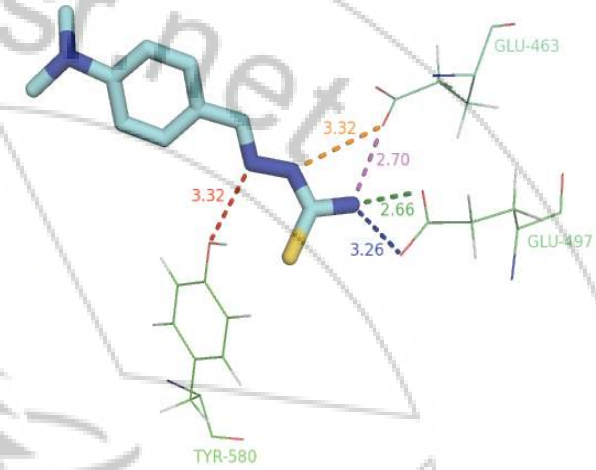


Figure 4: Interactions of Co-Crystal ligand and DBHC ligand with the protein

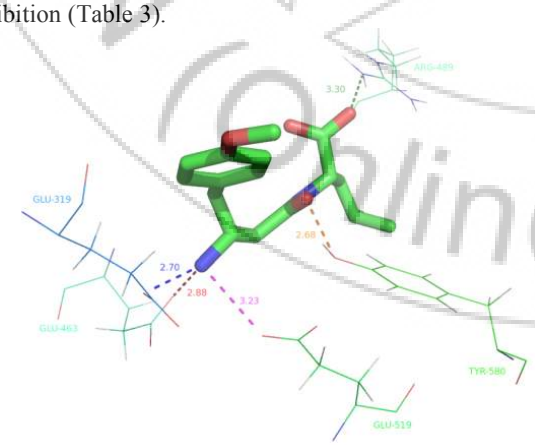
3.2 Docking Studies

Amino peptidase inhibitor was docked with DBHC using induced fit docking algorithm. The docking scores are shown in Table.3. The surface diagram shows the mode of binding energy for docked compounds in the active site of the protein amino peptidase (Figure 4).

The HDBC ligand very well bind with the GLU 463 & 497 and TYR 580 residues of the TTR protein. In DBHC ligand, all of the interactions are N-H…O type of interactions only and also the non-bonded interaction limits are within 2.5Å to 3.5Å which reveals that the DBHC ligand results in a strong inhibition (Table 3).

Table 3: Docking Score and Glide Energy

Ligand	D-H…A	Distance (Å)	Glide score	Glide energy (Kcal/Mol)
Co-crystal ligand	ARG-487(N-H…O)	3.30	-8.17	-45.898
	TYR-580(O-H…O)	2.68		
	GLU-519(O-H…N)	3.23		
	GLU-463(O-H…N)	2.88		
	GLU-319(O-H…N)	2.70		
DBHC ligand	TYR-580(O-H…N)	3.32	-5.38	-40.589
	GLU-463(O-H…N)	3.32		
	(O-H…N)	2.70		
	GLU-497(O-H…N)	2.66		
	(O-H…N)	3.20		



4. Conclusion

The title compound crystallizes in monoclinic crystal system, $P2_1/c$ space group. The crystal packing is stabilized by N-H…S and N-H…N type of intra and inter-molecular interactions The interaction study reveals that the molecule DBHC has good binding capability with the active site amino acids. The DBHC ligand is processed into *in vitro* studies for monitoring its inhibitory activity which can be used as potential drug.

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