Crystal structure and docking studies of (2R,5R,6S)-5-(4-chloro-2H-chromen-3-yl)-3-methyl-8-oxa-3-azatricyclo[7.4.0.0^{2,6}]trideca-1(9),10,12-triene-6-carbonitrile

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Abstract— **The chromen ring is not planar and adopts a sofa conformation. The phenyl ring attached to pyran ring is planar. The crystal structure is held together by extensive networks of both intramolecular and intermolecular hydrogen bonding. The crystal packing is stabilized by intra and intermolecular C—H…N, C-H…O & C-H…CL interactions. Molecular docking studies show that the chromone derivatives bind well in the active site pocket of transthyretin protein and interact with the active site amino acid residues, compare to the co-crystal ligand.**

Keywords- Chromen, Molecular Docking, Transthyretin

I. INTRODUCTION

Chromone derivatives are of interest as active natural products, because of their wide spectrum of biological activity, including antibacterial, antifungal, anti-allergic and anti-inflammatory activities [1]. We have recently focused on the structural modification of the chromone backbone by introduction of dibenzoylhydrazine substituents at the 3-position. The title compound (CHR) was investigated as a potential bioactive molecule.

Chromones are a group of naturally occurring oxygen containing heterocyclic compounds. They are widely distributed in plant kingdom and form the basic nucleus of important compounds such as anthocyanin and flavonoids. Chromones are also well known for their antimicrobial [2], antitumor and antiviral [3], activities. 3-Formylchromones are important synthons in synthetic chemistry for incorporating chromone moieties into other heterocyclic systems or for creating new heterocyclic systems based on chromone ring.

The chromones are also interesting as structural scaffolds and have been assigned as privileged structures for drug development [4]. Chromone derivatives, with different functionalized substituents, have for example been designed to be used as mimetics of short peptides [5].

II. MATERIALS & METHOD

A. 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.

B. Mechanics of Docking

To perform docking, the first requirement is the structure of the protein. Usually the structure has been determined in the lab using a biophysical technique such as x-ray crystallography, or less often, NMR spectroscopy. This protein structure and a database of potential ligands serve as inputs to a docking program. The success of a docking program depends on two components, namely, the search algorithm and the scoring function.

C. Synthesis

A mixture of (2*E*)-2-((2-formylphenoxy)methyl)-3-(4-chloro-2H-chromen-3-yl) acrylonitrile (1.2 mmol) and sarcosine (2 mmol) in acetonitrile (8 mL) was refluxed for 8 h. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated. Then the resulting crude mass was diluted with water (15 mL) and extracted with ethyl acetate (3 X 15 mL). The combined organic layer obtained was washed with brine (2 X 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified by column chromatography on silica gel ethyl acetate: hexanes (1:9) to afford the product as a colourless solid in good yield.

D. Data Collection & Structure Solving

Crystal X-ray diffraction is a very powerful and efficient analytical technique. The results obtained from this technique are most reliable and accurate. For compounds where suitable crystals were available, single crystal X-ray diffraction was carried out using Bruker Kappa APEX-2 CCD Diffractometer [6]. Cell refinement and data reduction was done using *SAINT [6]*. Program *SHELXS97* was used to solve structure. To refine structure *SHELXL97* (Sheldrick, 1997) was employed. All molecular graphics were generated using softwares *MERCURY* and *DIAMOND*. Single crystals suitable for X-ray diffraction were successfully grown for chromen compounds. The crystals analyzed had extensive networks of both intramolecular and intermolecular hydrogen bonds. The details of supramolecular structure and hydrogen bonding networks for each crystal are discussed.

III. Results and Discussion

A. X-Ray Crystallography

The crystal data and refinement parameters for chromen are given in Table.1. The *ORTEP* plot of chromen is given in Fig. 1. The phenyl ring (C17-C22) attached to chromen ring is planar. The chromen ring (C14-C18/O1) is not planar and adopts a sofa conformation [ϕ = 215.4(14) and θ = 115.2(13°] [7]. The carbonitrile side chain is almost linear, with a C-C-N angle of 177.0 (7)º.

The sum of the bond angles at N1[330.3(2)°] of the azatricyclo group is in accordance with sp3 hybridization (Beddoes et al., 1986). From the mean plane calculation chromen ring makes the dihedral angles of 79.1 (3)° with respect to the oxa azacyclo group. The maximum deviation of the chromen group atom is CL1 [0.403(2)°] and azacyclo group atom is N2 [3.048(6)°].

The phenyl ring (C1-C6) attached to pyran ring is planar. The six membered pyran ring also adopts a sofa conformation with puckering parameters (Cremer & Pople, 1975): *Q* = 0.455 (7) Å, θ = 51.8 (9)° and φ = 276.0 (11)°; the carbon atom C9 deviates from the mean plane by 0.654 (6) Å. All bond lengths and bond angles are within normal range [8].

The crystal structure is held together by extensive networks of both intramolecular and intermolecular hydrogen bonding. The crystal packing is stabilized by intra and intermolecular C-H…N, C-H…O & C-H…CL interactions as shown in Fig.2.

B. Docking Studies

Transthyretin(TTR) protein was docked with CHR using induced fit docking algorithm. The docking scores are shown in Table.3. The surface diagram shows mode of binding energy for docked compounds in active site of the protein PKB. (Fig.3.).

Chromene derivative very well bind with the GLU 54 and MET 13 residues of the TTR protein. GLU 54 bifurcated with the distance of 2.75 Å, 2.96 Å for N-H…O type interactions.

In all these complexes, the non-bonded interaction limits are within 2.5Å to 3.5Å which reveals that the ligand results in a strong inhibition (Fig.3.).

The above ligand are processed into *in vitro* studies for monitoring its inhibitory activity which can be used as potential anti-amyloidogenic drug for Transthyretin.

TABLE I. CRYSTAL DATA TABLE

Parameters	**chromen**
Empirical formula	C_{22} H_{19} Cl N_2 O_2
Formula weight	378.84
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 28.725(9) Å α = 90 º
	b = 18.580(6) Å β = 104.067(11)º
	c = 7.796(3) Å γ = 90 º
Volume	4036(2) A^3
Z, Calculated density	8, 1.247 Mg/m^3
Absorption coefficient	0.208 mm^{-1}
F(000)	1584
Crystal size	0.30 x 0.30 x 0.20 mm
Theta range for data collection	2.45 to 18.33 deg.
Limiting indices	-25<=h<=25, -16<=k<=16, -6<=l<=5
Reflections collected / unique	4379 / 1397 [R(int) = 0.0513]
Completeness to theta = 18.33	95.20%
Max. and min. transmission	0.9597 and 0.9404
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1397 / 0 / 245
Goodness-of-fit on F^2	0.983
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1381
R indices (all data)	R1 = 0.0883, wR2 = 0.1580
Largest diff. peak and hole	0.198 and -0.293 $e.A^{-3}$

TABLE II. POSSIBLE HYDROGEN BONDS AND NON-BONDED INTERACTIONS (Å AND º)

D-H...A	**d(D-H)**	**d(H...A)**	**d(D...A)**	**<(DHA)**
C(7)-H(7A)...N(1)^{i}	0.97	2.51	3.367(8)	147
C(19)-H(19)...O(1)^{ii}	0.93	2.54	3.414(13)	156

Symmetry equivalent positions: (i)½- x , ½- y, -z (ii)-x, -y, -z

TABLE III. DOCKING SCORE & GLIDE ENERGY

Ligand	**D-H…A**	**DISTANCE (Å)**	**Glide Score**	**Glide Energy (Kcal/mol)**
Co-Crystal	(MET 13) N-H…O	3.47	-1.861	-17.900
	(SER 117) O-H…O	3.33		
CHR	(MET 13) N-H…O	3.29	-2.080	18.989
	(GLU 54) N-H…O	2.75		
	(GLU 54) N-H…O	2.96		

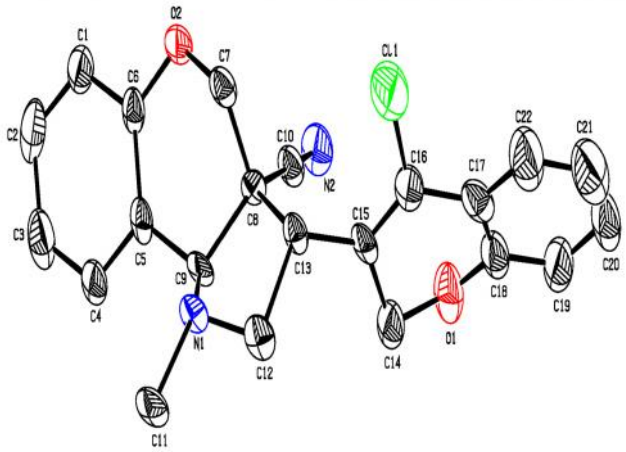

Figure 1. Perspective view of the molecule showing the thermal ellipsoids drawn at 30% probability level

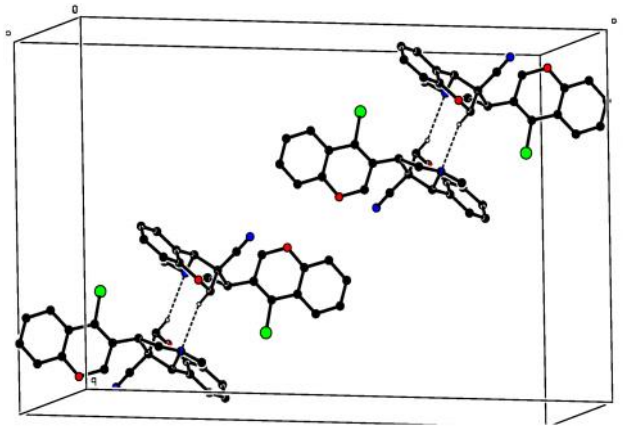

Figure 2. A view of the C-H···N hydrogen bonds (dotted lines) in the crystalstructure of the title compound

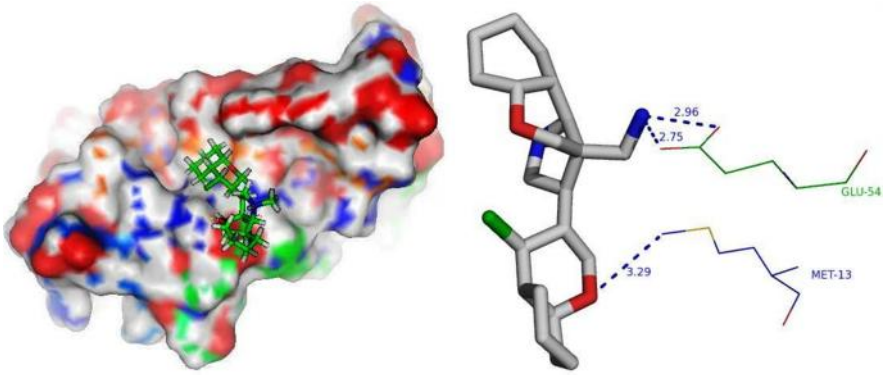

Figure 3. A view of surface diagram and chromene derivative interaction with the amino acid residues

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