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Insilico Binding Evaluation of Solid State Structures of Few Bromo Substituted Aryl Chalcones - Structure Based Lead Identification for Human Aldose Reductase Inhibition

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ABSTRACT

Solid state structure of a compound reveals the information on intermolecular forces experienced by the molecule. This information is helpful in understanding the molecular recognition process. One of the most important features in intermolecular forces is halogen bond which has been identified as similar to hydrogen bond. Halogen bond in solid state structures is being studied widely and interesting results are being delivered. Apart from directional specificity in crystal packing halogen bond has been identified to possess specificity in binding with several biological targets. We have performed docking studies on human aldose reductase (AR), a potential target for the treatment of diabetic complications. The study was performed using the solid state structure of the small molecules in the high resolution AR binding site. Study molecules were selected based on structural features of the co crystallized inhibitor (IDD594). Results suggested that the structural features of (2E)-1-(2-Bromo-phen-yl)-3-(4-bromo-phen-yl)prop-2-en-1-one are more satisfactory to be consider for lead development and optimization studies.

Keywords: Solid state structure, Halogen bond, Human aldose reductase, Best pose, Particular pose

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INTRODUCTION

Apart from numerous applications in basic research, crystal structure conformation of small molecules has always been the choice for binding energy calculations in molecular modeling during drug discovery process [1]. The reason is it provides coordinates for the most favorable stereo positions of the atoms in molecule. Since the crystal structure does not change usually after recrystallization one can predict that the intermolecular forces that are responsible for solid state structure may also exist in solutions for short intervals. Therefore, extrapolation of solid state intermolecular forces of organic molecules to target binding in the biological systems could be a good rational to use in drug discovery process.

A crucial process in drug discovery is lead identification. Starting from the earlier natural products screening to the advanced combinatorial high through put technology the process has undergone tremendous changes. Further, the advent of bioinformatics bought revolutionary concepts in drug designing with the aid of computational and statistical methods. Structure based drug design methodology in bioinformatics was found to be more rational and being used widely in drug discovery research [2]. The method involves the design and development of drug like molecule based on the information available on intermolecular non covalent interactions in the ligand-target complex. In order to understand the Supramolecular chemistry in ligand-target complex, primarily require a three dimensional structure of target or target with bound ligand. The later one is more helpful as the design process takes the advantage of both ligand and binding site structural features. We are interested in identification of lead molecule

to inhibit human aldose reductase (AR) based on the insights published from the crystal structure of human aldose reductase inhibitor complex.

Human aldose reductase (AR) is found to be a potential drug target for the treatment of diabetic complications [3]. Several inhibitors have been designed and few are in clinical trials [4]. The study using high resolution X-ray structure of IDD594-AR has given lucid information regarding the target binding pocket and substrate specificity [5, 6]. The study suggests that design of inhibitors for AR shall include halogen substitutions in order to get more specificity and potency.

Halogen bond is similar as that of the hydrogen bond. It is defined as A halogen bond in biomolecules can be defined as a short C-X...O-Y interaction (C-X is a carbon-bonded chlorine, bromine, or iodine, and O-Y is a carbonyl, hydroxyl, charged carboxylate, or phosphate group), where the X...O distance is less than or equal to the sums of the respective van der Waals radii [7]. Halogen bond in solid state structure is crucial for crystal packing. Though, excellent reviews of the same in biological system [7, 8] are there more research reports are required to understand the role of halogen bond in drug design process.

Versatile features of halogen bond and its directing specificity in AR binding inspired us to model the AR inhibition by few bromo- substituted aryl chalcones using the molecular modeling and analyze their interactions.

Chalocnes are widely distributed in nature and their derivatives are being widely studied as bioactive compounds [9-12]. They can be more readily synthesized and easily purified by crystallization. We have selected few chalcone derivatives from reported literature for this study. Criteria for selecting the molecules are availability of crystal structure coordinates and structural similarity with the potential inhibitor (IDD594). The selected molecules have bromine as halogen for specificity and the α,β unsaturated chain separating the two aromatic rings mimics the geometry and stereochemistry as that of IDD594. Exploring the possibilities of lead development from this set of molecules for AR inhibition is our objective.

MATERIALS AND METHODS

Preparation of Target Protein Structure

The crystal structure of Human Aldose Reductase (PDB: 1USO) taken in this study was retrieved from RCSB protein data bank (http://www.rcsb.org/pdb). The missing residues were corrected and the complexes bound to receptor molecule removed using Accelrys Discovery Studio Visualizer 2.5.5. The PDB files were energy minimized using ArgusLab. The non-essential water molecules were removed and polar hydrogens were merged.

Ligand Preparation

CIF files containing 3D coordinates of X-ray structure of the study chalcones (Table 1) were obtained as supplementary information of respective publications (13-20). In order to proceed for docking, the files were then converted to MOL format using Mercury software (http://www.ccdc.cam.ac.uk). Appropriate force field applied to them and then optimization was carried out using Argus Lab 4.0.1 (http://www.arguslab.com).

Docking simulations

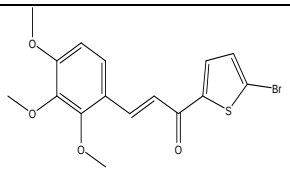
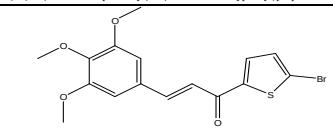
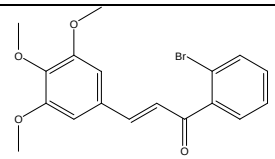
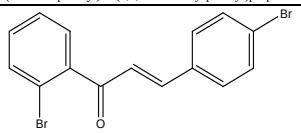
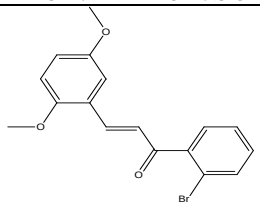
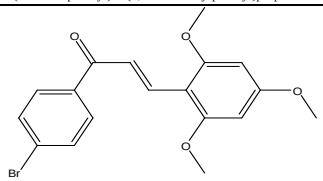
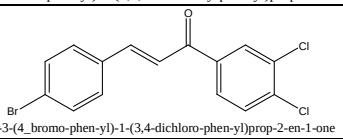
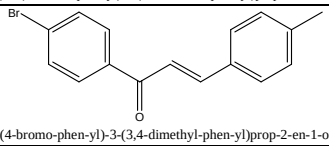
Docking experiments were performed using ArgusLab 4.0.1 (Mark A. Thompson, Planaria Software LLC, Seattle, WA, USA, http://www.arguslab.com) to find the reasonable binding geometries and explore the protein ligand interactions. Docking simulations were performed by selecting "ArgusDock" as the docking engine. The selected residues of the receptor were defined to be a part of the binding site. A spacing of 0.4 Å between the grid points was used and an exhaustive search was performed by enabling “High precision” option in Docking precision menu, "Dock" was chosen as the calculation type, "flexible" for the ligand and the AScore was used as the scoring function. At maximum 150 poses were allowed to be analyzed, binding site box size was set to 20 x 20 x 20 angstroms so as to encompass the entire active site. The AScore function, with the parameters read from the AScore.prm file was used to calculate the binding energies of the resulting docked structures.

All the compounds in the dataset were docked into the active site of 1USO, using the same protocol. After completion of docking, the docked protein (protein-ligand complex) was analyzed to investigate the type of interactions. The docking poses saved for each compound were ranked according to their dock score function. The poses were then analyzed for halogen bond interaction between ligand and the protein residues. The selection of halogen bond included pose was based on the criteria as defined for halogen bond in the published literature. The selected pose with halogen bond was compared with the pose having the highest dock score.

RESULTS AND DISCUSSION

Docking studies were performed for the study chalcones with the human aldose reductase protein using Argus labs software. According to the docking results the chalcone (M1) (2E)-1-(5-bromothiophen-2yl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one at its best ligand pose showed 3 hydrogen bonds with Trp111, His110 and Leu300 residues of the protein and the distances were found to be 2.99995A^0, 2.462599A^0 and 2.861413A^0 respectively (Table 1, Figure 1). No significant halogen bond was identified in this pose. At a particular pose this chalcone showed halogen bond with the residue Thr113 at a distance of 2.732187A^0 and a hydrogen bond with the residue His110 at a distance of 2.987373A^0. (Table 2, Figure 2)

Table 1: Binding interactions at best pose

Molecule	Structure	Dock Score	Hydrogen Bond		Halogen Bond Br---O (Thr113)
			Residue	Distance	Distance
M1	 (2E)-1-(5-bromothiophen-2-yl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one	-12.10	O---HO(Trp111) O---HO(HIS110) O---HO(Leu300)	2.999 A^0 2.462 A^0 2.861 A^0	NS
M2	 (2E)-1-(5-bromothiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one	-12.93	O---HO(Trp113) O---HO(Thr113)	2.391 A^0 2.821 A^0	NS
M3	 (2E)-1-(2-bromo-phen-yl)-3-(3,4,5trimethoxy-phen-yl)prop-2-en-1-one	-11.76	O---HO(Cys298) O---HO(Trp113) O---(HOH2062)	2.951 A^0 2.986 A^0 2.866 A^0	3.014A^0
M4	 (2E)-1-(2-bromo-phen-yl)-3-(4-bromo-phen-yl)prop-2-en-1-one	-14.50	O---HO(Cys303)	2.999 A^0	3.304A^0
M5	 (E)-1-(2-bromo-phen-yl)-3-(2,5-dimethoxy-phen-yl)prop-2-en-1-one	-13.04	O---HO(Cys303) O---HO(His110) O---HO(Trp111)	2.926 A^0 2.537 A^0 2.999 A^0	3.182A^0
M6	 (E)-1-(4-bromo-phen-yl)-3-(2,4,6trimethoxy-phen-yl)prop-2-en-1-one	-12.33	O---HO(His110) O---HO(Trp111)	2.999 A^0 2.300 A^0	NS
M7	 (E)-3-(4_bromo-phen-yl)-1-(3,4-dichloro-phen-yl)prop-2-en-1-one	-14.17	O---HO(Trp111)	-2.321 A^0	2.232A^0
M8	 1-(4-bromo-phen-yl)-3-(3,4-dimethyl-phen-yl)prop-2-en-1-one	-15.28	O---HO(Trp111)	2.222 A^0	NS

NS: No Significance

Table 2: Binding interactions at particular pose

Molecule	Dock Score	Hydrogen Bond		Halogen Bond Br---O(Thr113)
		Residue	Distance	Distance
M1	-10.85	O---HO(Trp111)	2.987 A^0	2.732 A^0
		O---(HOH2062)	2.388 A^0	
M2	-11.98	O---HO(His110)	2.951 A^0	3.832 A^0
		O---HO(Cys80)	2.574 A^0	
		O---HO(Trp111)	2.609 A^0	
M6	-11.55	O---HO(Trp80)	2.999 A^0	2.373 A^0
		O---HO(Trp111)	2.548 A^0	
		O---(HOH2062)	2.359 A^0	
M8	-12.89	NS	NS	2.163 A^0

NS: No Significance

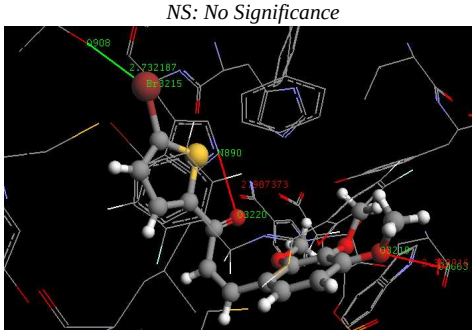


Figure 1: Best Pose of M1 in AR binding site

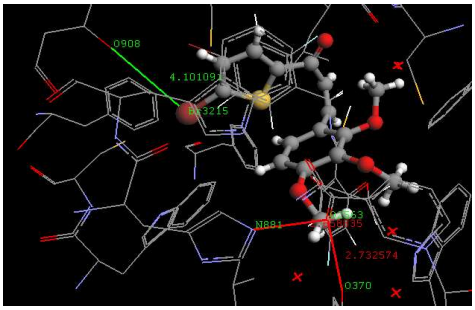


Figure 2: Particular Pose of M1 in AR binding site

(2*E*)-1-(5-bromothiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one – (M2) at its best ligand pose showed 2 hydrogen bonds with Thr113, Trp113 residues of the protein and the distances were 2.82165 A^0 and 2.391250 A^0 respectively (Table 1, Figure 3). No halogen interaction was observed at this pose. At a particular pose M2 showed a weak halogen bond with the residue Thr113 at a distance of 3.832698 A^0 and 2 hydrogen bonds between His110, Cys80 residues of the protein and the ligand whose distances were 2.951521 A^0 and 2.574232 A^0 respectively (Table 2, Figure 4).

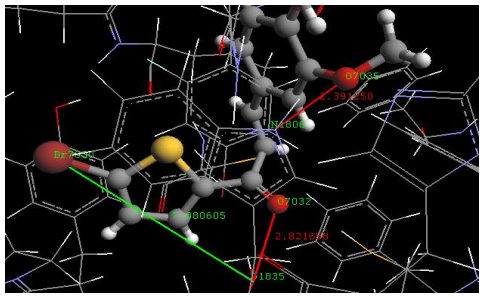


Figure 3: Best Pose of M2 in AR binding site

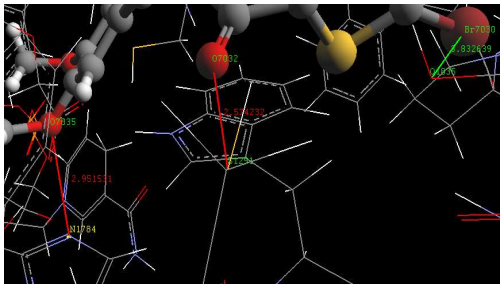


Figure 4: Particular Pose of M2 in AR binding site

(2E)-1-(2-Bromo-phen-yl)-3-(3,4,5-trimeth-oxy-phen-yl)prop-2-en-1-one-(M3) at tits best ligand pose showed 3 hydrogen bonds with Cys298, Trp20 and HOH2062 residues of the protein and the distances were found to be 2.951673 A^0, 2.986509 A^0 and 2.866271 A^0 respectively (Table 1, Figure 5). The distance between the Br atom of the chalcone and the O atom of the residue Thr113 in the protein was found to be 3.014912 A^0. This signifies the presence of halogen bond interaction.

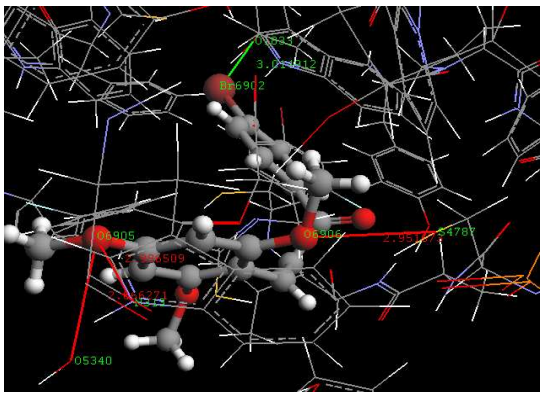


Figure 5: Best Pose of M3 in AR binding site

(2E)-1-(2-Bromo-phen-yl)-3-(4-bromo-phen-yl)prop-2-en-1-one-(M4) at its best ligand pose showed a hydrogen bond was found with Cys303 residue of the protein and the distance was found to be 2.999500 A^0. The distance between the Br atom of the chalcone and the O atom of the residue Thr113 in the protein was found to be 3.304176A^0. (Table 1, Figure 6) This signifies the presence of weak halogen bond.

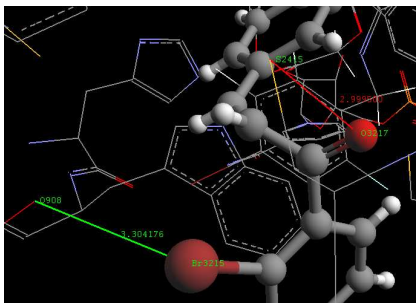


Figure 6: Best Pose of M4 in AR binding site

(E)-1-(2-Bromo-phen-yl)-3-(2,5-dimeth-oxy-phen-yl)prop-2-en-1-one-(M5) at its best ligand pose showed a dock score of -13.04. In this pose 3 hydrogen bonds were found with Cys300, His110, Trp111 residues of the protein and the distances were 2.926579A^0, 2.537842 A^0, 2.999873 A^0.The distance between the Br atom of the chalcone and the O atom of the residue Thr113 in the protein was found to be 3.182219 A^0. This signifies the presence of halogen bond interaction. (Table 1, Figure 7)

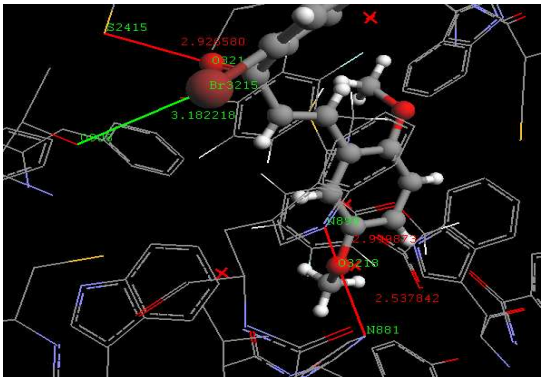


Figure 7: Best Pose of M5 in AR binding site

(E)-1-(4-Bromo-phen-yl)-3-(2,4,6-trimethoxy-phen-yl)prop-2-en-1-one-(M6) at its best ligand pose showed 2 hydrogen bonds with His110, Trp111 residues of the protein and the distances were 2.999864 A^0, 2.300405A^0 respectively (Table 1, Figure 8). No halogen bond interaction was observed. M6 at a particular pose showed a strong halogen bond between the Br atom of the chalcone and the 'O' atom of the residue Thr113 with a distance of 2.373623A^0. 3 hydrogen bonds were also seen in this pose with Trp20, HOH2062, Trp111 residues of the protein and the distances were 2.999407A^0, 2.359629 A^0 and 2.548627 respectively (Table 2, Figure 9)

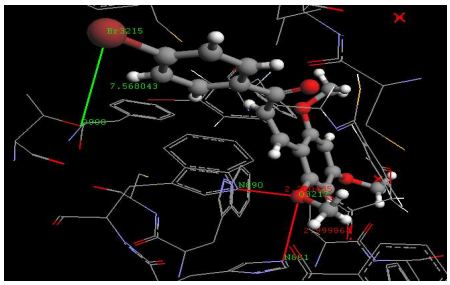


Figure 8: Best Pose of M6 in AR binding site

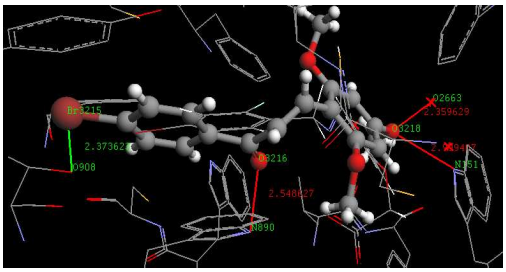


Figure 9: Particular Pose of M6 in AR binding site

(E)-3-(4-Bromo-phen-yl)-1-(3,4-dichloro-phen-yl)prop-2-en-1-one (M7) at its best ligand pose showed a hydrogen bond with Trp111 residue of the protein and the distance was found to be 2.321085A^0. Potential halogen bond as similar to M6 was also found at a distance of 2.232676A^0 from Thr113 (Table 1, Figure 10)

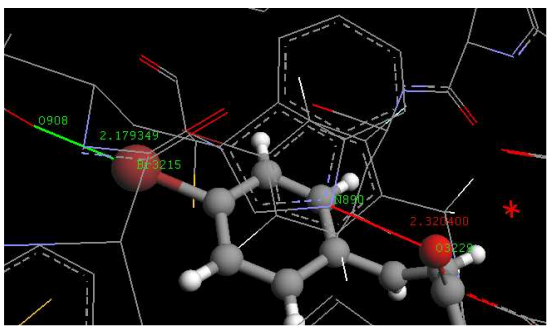


Figure 10: Best Pose of M7 in AR binding site

(E)-1-(4-Bromo-phen-yl)-3-(3,4-dimethyl-phen-yl)prop-2-en-1-one (M8) at its best ligand pose showed highest dock score among the series. In this pose a hydrogen bond was found betweenThr113 residue of the protein and the ligand, the distance was 2.222305A^0. (Table 1, Figure 11) No halogen bond interaction was observed. At a particular pose this chalcone showed a halogen bond with the residue Thr113 at a distance of 2.163506A^0 without any other significant interactions (Table 2, Figure 12)

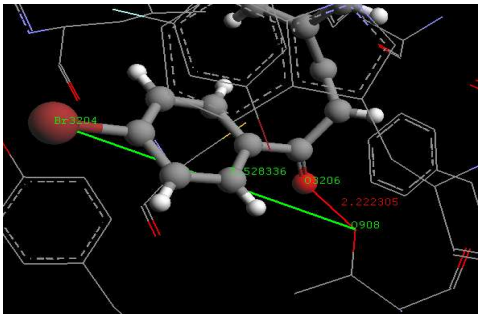


Figure 11: Best Pose of M8 in AR binding site

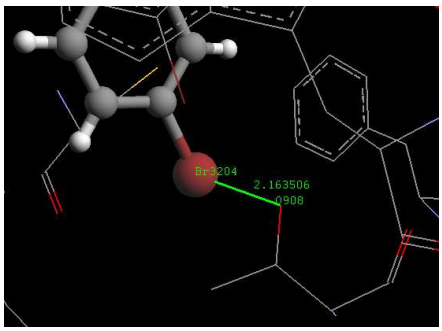


Figure 12: Particular Pose of M8 in AR binding site

CONCLUSION

M1, M2, M6 & M8 have shown potential halogen bond interaction in their best dock score pose without any significant halogen bond. However, the halogen bond showed by M8 at particular pose was significant and strongest in the series. Though M8 has the least number of intermolecular forces it possessed highest dock score due to hydrophobic attractions in the binding pocket. M3, M4, M5 & M7 have potential hydrogen bonds along with significant halogen bond interaction in their best pose. Among these M7 has the strongest interactions, M4 has highest dock score and M5 has highest number of interactions. M4 & M7 have close dock score values due to similar hydrophobicity and equal number of interactions they made with the AR binding site. M7 is comparatively more lipophilic than M4 due to one excess halogen. Considering the determinant effect of partition coefficient value on efficacy, we conclude that the structural features of (2E)-1-(2-Bromo-phen-yl)-3-(4-bromo-phen-yl)prop-2-en-1-one (M4) would be more promising to be considered for lead development and optimization studies.

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