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Research Article

Molecular docking studies of ceftriaxone sodium with apoptosis protein in colorectal cancer

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ABSTRACT

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand—protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Docking study was performed by Schrodinger-Maestro 9.3.5 Version.In the present study was performed to identify the binding energy, H bond interaction, hydrobhobicity and lipophobicity of ligand ceftriaxone sodium with Apoptosis protein (which is involved in colon cancer). While performing docking simulation, information on feasible conformations of the ligand within the protein binding site can be obtained. This information can also reflect the nature and quality of the interaction. The proteins like caspase-8 (PDB Id: 1QDU), anti-apoptotic protein Bcl-xL (PDB Id: 2O1Y), M20 family metallo peptidase (PDB Id: 2POK), caspase-3 (PDB Id: 2XZT) which displayed superior binding interactions and which possessed highest inhibitory activity among the various selected receptors.

Keywords: ACD; Chem sketch; Caspase cascade; Schrodinger-Maestro

INTRODUCTION

Apoptosis, or programmed cell death, is a highly regulated process important in embryonic and immune system development and tissue homeostasis (Susan Elmore., 2007). Initiation, commitment, and execution are the three fundamental steps of apoptosis (Susin,S *et al.*, 2000). Survival of cancer cell is influenced by the interactions between pro- anti-apoptotic proteins. In normal cell death signals generated by Bak and Bax, cytochrome c is released into the cytosol, leading to the activation of the caspase cascade and the induction of the cell death. Developing novel molecules that promote apoptosis by targeting both the intrinsic and extrinsic apoptotic pathways advances our understanding of the mechanisms behind tumour cell proliferation, which may also lead to the development of effective cancer therapies.

In modern drug designing, molecular docking is routinely used for understanding drug receptor interaction of two molecules and to find the best orientation of ligand which would from a complex with over al minimum energy. The beta lactam antibiotics play an essential role nitrating bacterial infections while demonstrating selectivity for prokaryotic cells.

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Certain N-methyl thio- substituted beta lactam antibiotics had DNA damaging and apoptosis inducing activities in various tumour cells (Aslamuzzaman Kazia *et al.,* 2004). Apoptosis is triggered through two signalling pathways. The intrinsic, or mitochondrial pathway is initiated from within the cell. The intrinsic pathway hinges on the balance activity between pro and anti apoptotic signals of the Bcl2 family. The extrinsic pathway begins outside the cell through activation of pro-apoptotic receptor agonists, these are activated by molecules known as pro-apoptotic ligands Preclinical studies that members of the Bcl-2 family regulate the permeability of the mitochondrial membrane and determine whether a pro-or anti apoptotic signal will be inside the cell (Susan Elmore.,2007).

The computational approach to search for a ligand that is able to fit both geometrically and energetically in the binding site of the receptor is called *insilico* or molecu---lar docking analysis (Sivakumari K *et al.*, 2010). The present study is aimed to perform a docking analysis using third generation cephalosporin antibiotic, Ceftri--axone sodium into the Apoptosis protein to determine the probable binding model for anti- human colon can---cer.

MATERIALS AND METHODS

Preparation of protein structure

The protein data bank is the global archive for infor---mation about the 3D structure of bio macro molecule and their complexes (Pappu srinivasan *et al.*, 2011). The following Antiapoptotic Proteins such as Bcl-2(B-

Table 1: Lipinski's properties of Ceftriaxone sodium

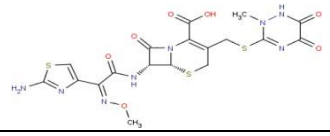
Ligand molecule	Molecular weight [g/mol]	Molecular Formula	Xlogp3 value	H-bond donor	H-bond acceptor	Structure
Ceftriaxone Sodium	554.580	C18H18N8O7S3	-1.79	4	12	

Table 2: Docking result of the legend Ceftriaxone sodium with apoptosis protein

Protein	Amino acid/Water	Atoms in amino acid	H-bond length (Å)	H-bond	Dock Score
caspase 8	ARG	O	2.695A^0	**5**	**-8.1**
	ALA	N	1.988A^0		
	GLY	H	1.877A^0		
	THR	O	1.868A^0		
	GLN	O	1.898A^0		
BcL-xl-B-cell lymphoma-extra large	GLU	H	2.963A^0	**3**	**-6.5**
	TYR	H	2.157A^0		
	ASN	O	1.977A^0		
Metallo peptidase	ARG	O	3.71 A °	**4**	**-7.4**
	SER	N	3.89 A °		
	THR	O	3.02 A °		
	H2O	O	3.04 A °		
Caspase 3	ASN	O	2.157A^0	**5**	**-9.3**
	ASN	H	1.977A^0		
	ASP	N	1.867A^0		
	GLY	O	2.963A^0		
	GLU	H	1.898A^0		

cell lymphoma 2), Bcl-XL (B-cell lymphoma-extra large), Mcl-1(Induced myeloid leukemia cell differentiation protein) and Proapoptotic proteins such as Bax (Bcl2 associated X Protein), Bak (Bcl-2 homologous antagonist/killer) Bad (Bcl-2-associated death promoter) and Apaf-1 (Apoptotic peptidase activating factor 1),Caspase-9 Caspase-8 Caspase-3 (*c*ysteine-*asp*artic prote*ases*) proteins are involved in apoptosis program (Kwak EL *et al*., 2007). The 3D structure of the proteins were downloaded from protein data bank (http://www.rcsb.org/pdb/home/home.do) with the specific resolution and the Protein data bank ID for those proteins areP53 : 1TUP, caspase-8 :1QDU, Bcl-xL:2O1Y, 2POK, caspase-3 : 2XZT.

Preparation of ligand structure --- Chem Sketch

ACD/Chemsketch is the powerful chemical drawing and graphics package from ACD/Labs software which will draw molecular structures reaction and calculate chemical properties very quickly and easily. The three dimensional structure of ligand were drawn by chem sketch. (Ramesh kumar D *et al.,* 2012).

Lipinski's analysis

Lipinski's rule says that to evaluate drug likeness and determine the pharmacological activity .The Lipinski's properties like molecular weight, log p, number of hy---drogen bond donors and acceptors (Lipinski's C A., 2000) Lipinski's parameters to satisfy the retrieved ligand were analysis using Pub Chem tool. Table1

Molecular Docking Study

Docking is a computational technique which is used to determine the interaction between ligand and the re---ceptor based on dock score. The H bond length, num-ber of H bonds and scoring functions are used to access the confirmation of the probable protein binding site. The inhibitor and target protein was geometrically op---timized and docked using docking engine Schrodinger-Maestro 9.3.5 Version. The single ligand (ceftriaxone sodium) was separately docked with a targeted 10 proteins.

RESULTS AND DISCUSSION

Molecular docking study shows that the inhibitory pathway of the potential drug target against colon can---cer using bioinformatics tool (Warren G L *et al*., 2000). Docking simulation is a popular approach for the preliminary screening in structure based drug design. By performing docking simulation, information on feasible conformations of the ligand within the protein binding site can be obtained. This information can also reflect the nature and quality of the interaction. In our study, the grid box for docking simulation was built with enough size to enable probing into the binding with targeted proteins. The proteins like caspase-8 PDB

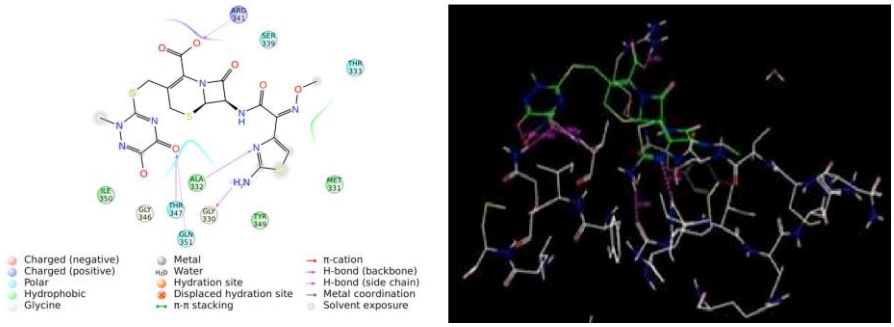


Figure 1: Caspase-8

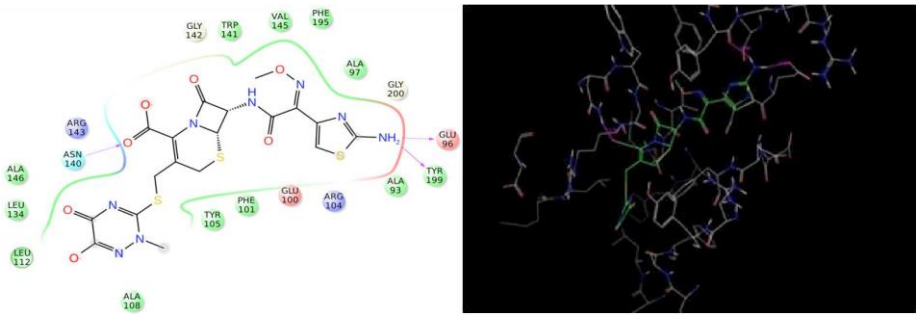


Figure 2: B-cell lymphoma-extra large

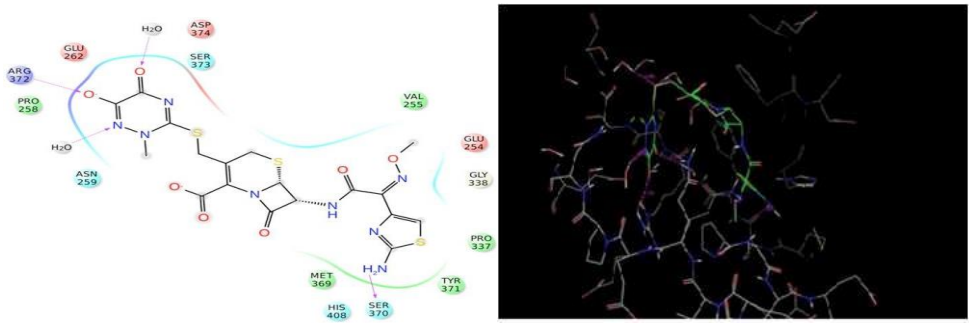


Figure 3: Metallo peptidase

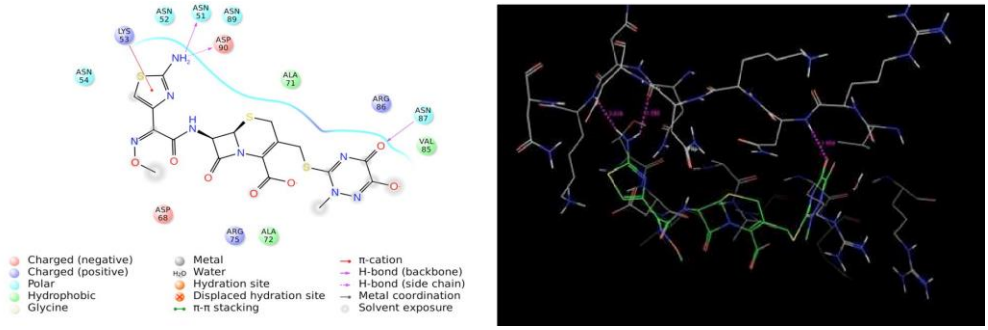


Figure 4: Caspase 3

Id: 1QDU (Fig.1), anti-apoptotic protein Bcl-xL PDB Id: 2O1Y (Fig.2) M20 family metallo peptidase PDB Id: 2POK (Fig.3), caspase-3 PDB Id: 2XZT (Fig.4) which displayed superior binding interactions and which possessed highest inhibitory activity among the various selected receptors (Table 2). This simulation may assist to reveal binding orientation and interaction of these molecules with amino acid residues composing active site gorge in these receptors indicated that hydrogen bonding, hydrophobic and mild polar interactions and Pi cations are the four major interactions incorporating the attachment of this ligand to receptors. According to Trapani *et al*., (1992) a single hydrogen bond would not be expected to support a drug-receptor interaction alone, but when multiple hydrogen bonds, high dock score value and low bond length are formed between drugs and receptor, a significant amount of stability is conferred upon the drug-receptor interaction

CONCLUSION

The protein-ligand interaction plays a significant role in structural based drug designing and it is used to reduce cost and time in drug discovery. (Sheng *et al.,* 2010). Present study identified through docking and binding

interactions of various anticancer targeted receptors with a single ligand ceftriaxone, for the evaluation of most active target receptor for the interaction of a ligand ceftriaxone. In these studies various intermolecular interactions were observed. In this study we identified ceftriaxone sodium has major affinity on four receptors. i.e. The proteins like caspase-8 PDB Id: 1QDU, anti-apoptotic protein Bcl-xL PDB Id: 2O1Y, M20 family metallo peptidase PDB Id: 2POK, caspase-3 PDB Id: 2XZT which displayed superior binding interactions and which possessed highest inhibitory activity among the various selected receptors. Identifying the location of ligand binding sites on a protein, *de novo* drug design and structural identification and comparison of functional sites were the fundamental importance in molecular docking Laurie A T R 2006 Further *in-vivo* and *in-vitro* approaches are required to elucidate the molecular mechanisms of this compound to act as potent drug against colon cancer.

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