

Molecular docking studies of deacetyl-bisacodyl with intestinal sucrase-maltase enzyme

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Abstract

Molecular docking of sucrase-isomaltase with ligand deacetyl-bisacodyl when subjected to docking analysis using docking server, predicted in-silico result with a free energy of -3.36 Kcal/mol which was agreed well with physiological range for protein-ligand interaction, making bisacodyl probable potent anti-isomaltase molecule. According to docking server Inhibition constant is 5.98Mm which predicts that the ligand is going to inhibits enzyme and result in a clinically relevant drug interaction with a substrate for the enzyme. Hydrogen bond with bond length 3.45Å is formed between Pro 64 (A) of target and N₁ of ligand, which is again indicative of the docking between target and ligand. Excellent electrostatic interactions of polar, hydrophobic, pi-pi and Van der waals are observed. The protein-ligand interaction study showed 6 amino acid residues interaction with the ligand

Keywords: Docking, sucrase isomaltase, bisacodyl, docking server.

1. Introduction

Docking technique is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Understanding the preferred orientation can be used to predict the strength of binding affinity between two molecules. As such, docking studies can be used to identify the structural features that are important for binding and for *in silico* screening efforts in which suitable binding partners can be identified.

Docking is a program where two proteins, or a protein known as 'receptor' and chemical entity known as 'ligand' are allowed to interact with each other on a software to analyze the interactions occurring between the receptor and ligand. The interaction can be analyzed by evaluating several parameters like Free energy of binding (kcal/mol). Binding energy is a measure of the affinity of ligand-protein complex, which suggests the energy possessed by the complex formed between the receptor-ligand, indicative of the loss in energy during complex formation. Lesser the energy more stable is the

complex formed. Total energy is the sum of changes of all energetic terms included in scoring function of ligand or protein upon binding, plus the changes upon binding of the entropic terms. Electrostatic energy is the change on the electrostatic non bounded energy of ligand or protein upon binding. Existence of hydrogen bonds also stabilize complex, the more number of bonds are formed, and higher is the stability of the complex.

The physiologic process and proper function of the digestive system requires intimate participation from both the nervous, endocrine systems and the gastrointestinal system. The enzymes responsible for the terminal stage of digestion are tethered as integral membrane proteins in the plasma membrane of the enterocyte. These are referred to as brush border enzymes namely Glucoamylase, Sucrase-Isomaltase, Lactase and Peptidases.

Sucrase-isomaltase is a small intestinal enzyme that work concurrently with maltase-glucoamalyse to hydrolyze the mixture of linear alpha-1,4- and branched alpha-1,6-oligosaccharide substrates. The N-terminal catalytic domain of this

enzyme has a broader specificity for both alpha-1,4- and alpha-1,6-oligosaccharides. Senna and bisacodyl are the most commonly used stimulants for constipation.

Bisacodyl is a laxative which is being used throughout the world. It acts on the mesenteric plexus of the colon and stimulate peristaltic contractions [1,2] which decreases transit time [3,4] due to decreased water absorption. In the present study, docking of deacetylbisacodyl with intestinal sucrase-maltase enzyme was investigated and communicated.

2. Experimental

In the present study, the X-ray crystal structure of 3lpo - *HYDROLASE* Sucrase-isomaltase was obtained from Protein Data Bank [5]. Docking calculations were carried out using Docking Server. Docking calculations were carried out on 3lpo - *HYDROLASE* Sucrase-isomaltase protein model. The description of a protein three dimensional structure as a network of hydrogen bonding interactions (HB plot) [6] was introduced as a tool for exploring protein structure and function.

Figure 1: Docking for deacetylbisacodyl to 3lpo – HYDROLASE sucrase-isomaltase

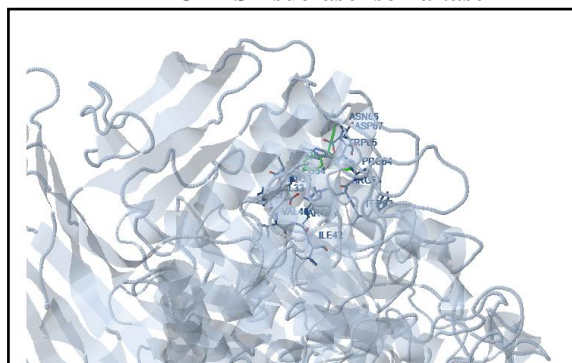


Figure 2: Interaction between the ligand and the enzyme sucrase

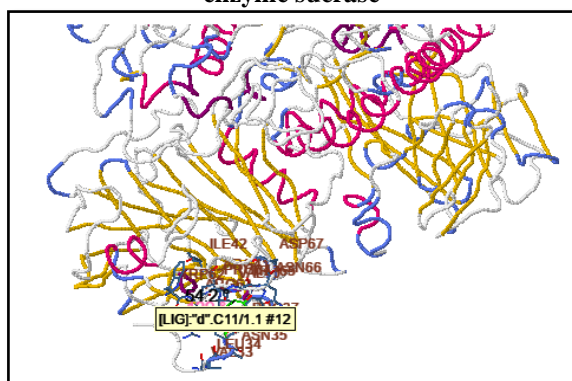


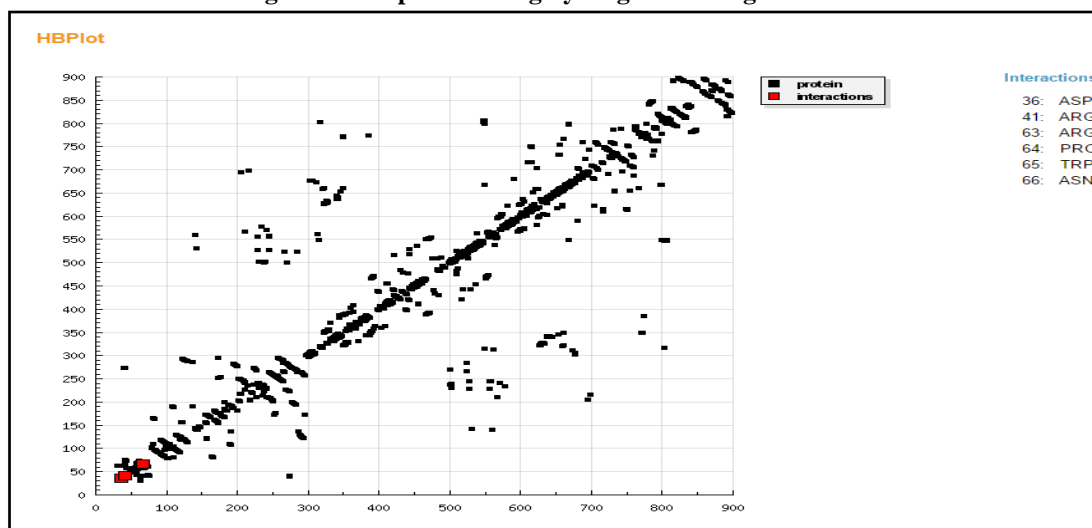
Table 1: Molecular Docking energy level table

Rank	Est. Free Energy of binding	Est. Inhibition Constant, KI	vdW+ Hbond+desolv Energy	Electronic Energy	Total intermolec. energy	Frequency	Interact. Surface
1.	-3.03kcal/mol	5.98 mM	-4.41 kcal/mol	-0.06 kcal/mol	-4.47 kcal/mol	10%	462.737
2.	-2.90 kcal/mol	7.47 mM	-4.31 kcal/mol	0.06 kcal/mol	-4.37 kcal/mol	20%	406.402
3.	-2.75 kcal/mol	9.65 mM	-4.22 kcal/mol	-0.00 kcal/mol	-4.22 kcal/mol	10%	460.617
4.	-2.67 kcal/mol	11.02 mM	-4.23 kcal/mol	-0.02 kcal/mol	-4.25 kcal/mol	20%	400.015
5.	-2.60 kcal/mol	12.52 mM	-4.10 kcal/mol	-0.05 kcal/mol	-4.15 kcal/mol	10%	423.934
6.	-2.46 kcal/mol	15.66 mM	-3.98 kcal/mol	+0.00 kcal/mol	-3.98 kcal/mol	20%	411.222
7.	-2.43 kcal/mol	16.65 mM	-3.92 kcal/mol	+0.00 kcal/mol	-3.92 kcal/mol	10%	428.181

Table 2: Decomposed Interaction Energies in kcal/mol

Hydrogen bonds	polar	Hydrophobic	Pi-pi	Other
N1 (15) - PRO64 [3.45] (O)	O2 (21) - ASP36 [2.93] (OD2)	C16 (17) - PRO64 [3.27] [CD]	C12 (12) - TRP65 [3.32] (CE3,CZ3)	H15 (36)- ASP 36 [3.06] (CB,CG)
	H15 (36) - ASP36 [2.07] (OD2)	C18(19)- PRO64 [3.58] (CD)	C10 (10) - TRP65 [3.82] (CE3,CZ3)	O2 (21) - ASP36 [3.82] (CG)
	O2 (21) - ARG41 [3.45] (NH2)		C13 (13) - TRP65 [3.40] (CZ3)	C13 (13) - ASP36 [3.89] (OD2)
	H15 (36) - ARG41 [3.05] (NH2)			C13 (13) - ARG41 [3.65] (NH2)
	H15 (36) - ARG63 [3.84] (CD,NH1)			C12 (12) - ARG41 [2.97] (NH2)
	O1 (20) - ASN66 [3.72] (OD1)			C12 (12) - ARG63 [3.46] (CD, CG)
	H14 (35) - ASN66 [2.85] (ND2, OD1)			C10 (10) - ARG63 [3.52] (CD, CD)
				O2 (21) - TRP65 [3.71] (CZ3)
				H14 (35) - ASN66 [3.00] (CG)
				C2 (2) - ASN66 [3.18] (OD1)
				C4 (4) - ASN66 [3.87] (OD1)

Figure 3: HB plot showing hydrogen bonding interaction



3. Results and Discussion

The interaction between the ligand and the target enzyme are presented in the figures (1 & 2). Tables 1 & 2 shows the interaction energies involved in the binding of the ligands to the enzymes. According to docking server Inhibition constant is 5.98Mm. K_i is helpful in predicting that a particular ligand is going to inhibit a particular enzyme and result in a clinically relevant drug interaction with a substrate for the enzyme. K_i is reflective of the binding affinity. If a K_i is much larger than the maximal plasma drug concentrations a patient is exposed to from typical dosing, then that drug is not likely to inhibit the activity of that enzyme. Smaller the K_i , the smaller amount of medication is needed in order to inhibit the activity of that enzyme. The value obtained here is 5.98mM, which lies well within the limits. According to docking server (Table 2), hydrogen bond with bond length 3.45 \AA is formed between Pro 64 (A) of target and N_1 of ligand, which is again indicative of the docking between target and ligand. Excellent electrostatic interactions of polar, hydrophobic, pi-pi and Vander walls interactions are observed (Table 2). ADME data suggest the Ligand shows CYP2C19, CYP2C9CYP3A4P-glycoprotein inhibition. HB plot explores the amino acid residues involved in stabilizing protein structure. The protein–ligand interaction showed 6 amino acid residues interaction with the ligand (36: ASP 41: ARG 63: ARG 64PRO 65TRY 66ASN). The interaction of ligand and protein was generated and is depicted in HB plot (Figure 3). The energy and interaction details have been developed using Docking server. The free energy (ΔG) of interaction is -3.03 Kcal/mol , which is in good agreement with physiological protein-ligand interaction range of -2.00 Kcal/mol to -6.00 Inhibitions constant (K_i) 5.98 Mm is favorable for the

interaction. Docking results give binding site analysis for 6 amino acids, with the ligand which shows precise conformity. The ligand bisacodyl interacted well with the protein isomaltase in the docking grid.

4. Conclusions

Molecular docking of sucrase-isomaltase with ligand deacetyl bisacodyl when subjected to docking analysis using docking server, predicted in-silico result with a free energy of -3.36 Kcal/mol which agreed well with physiological range for protein-ligand interaction, making bisacodyl probable potent anti-isomaltase molecule.

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