Protein Engineering
Review 3
Molecular Docking

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Molecular docking :

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.

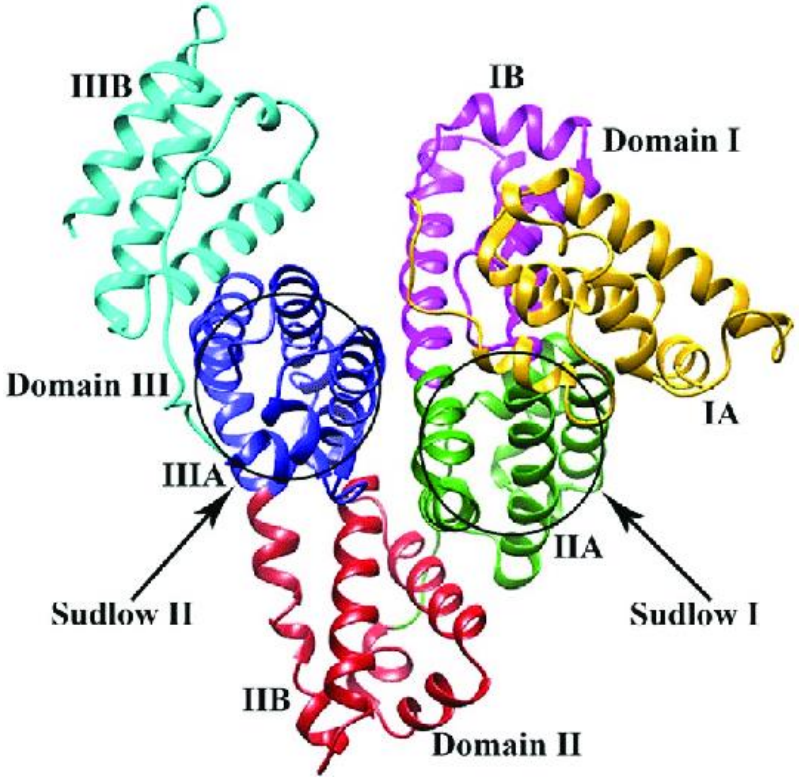
Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization.

Protein : Human serum albumin (HSA)

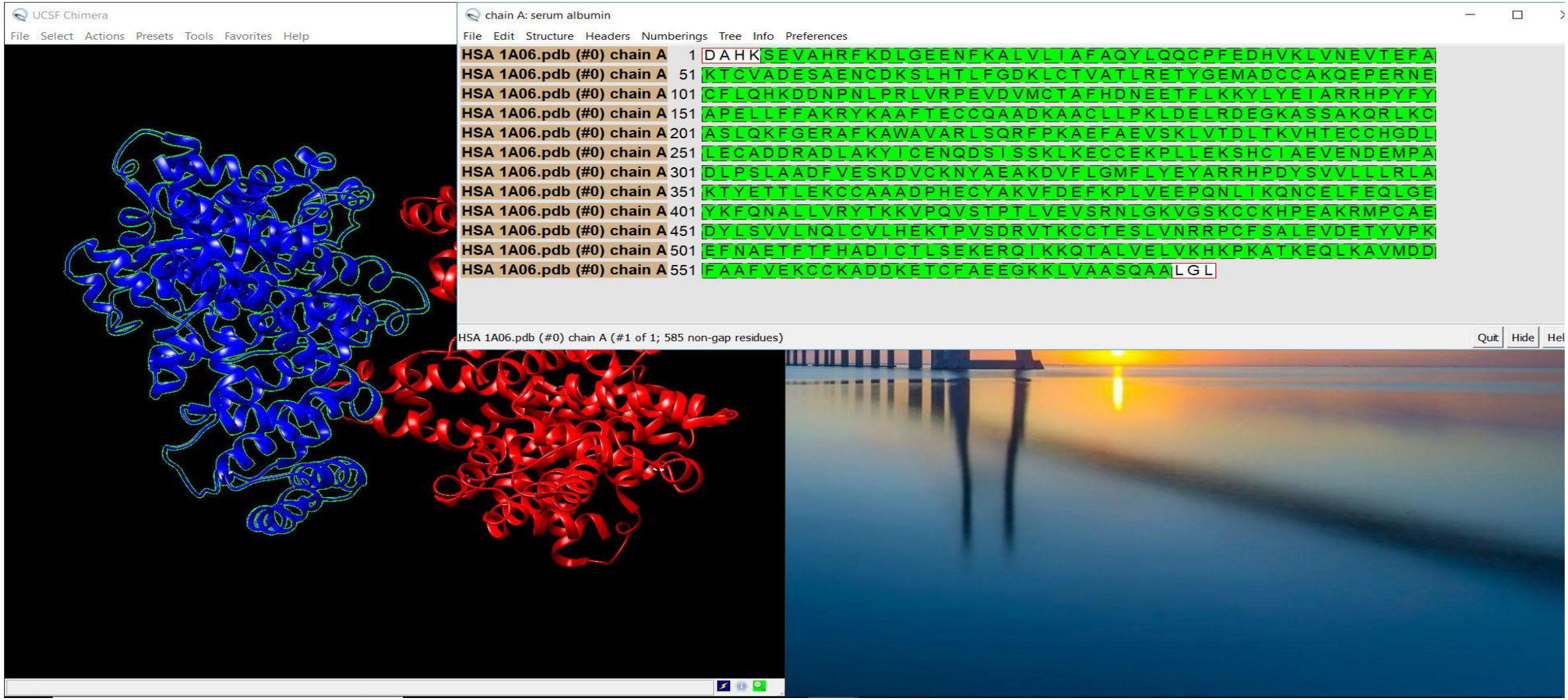
It is a serum albumin found in human blood and it is the most abundant protein in the human blood plasma. It constitutes about half of serum protein. It is produced in the liver. It is soluble and monomeric.

It transports hormones ,fatty acids and other compounds ,buffers ,PH, and maintains pressure.

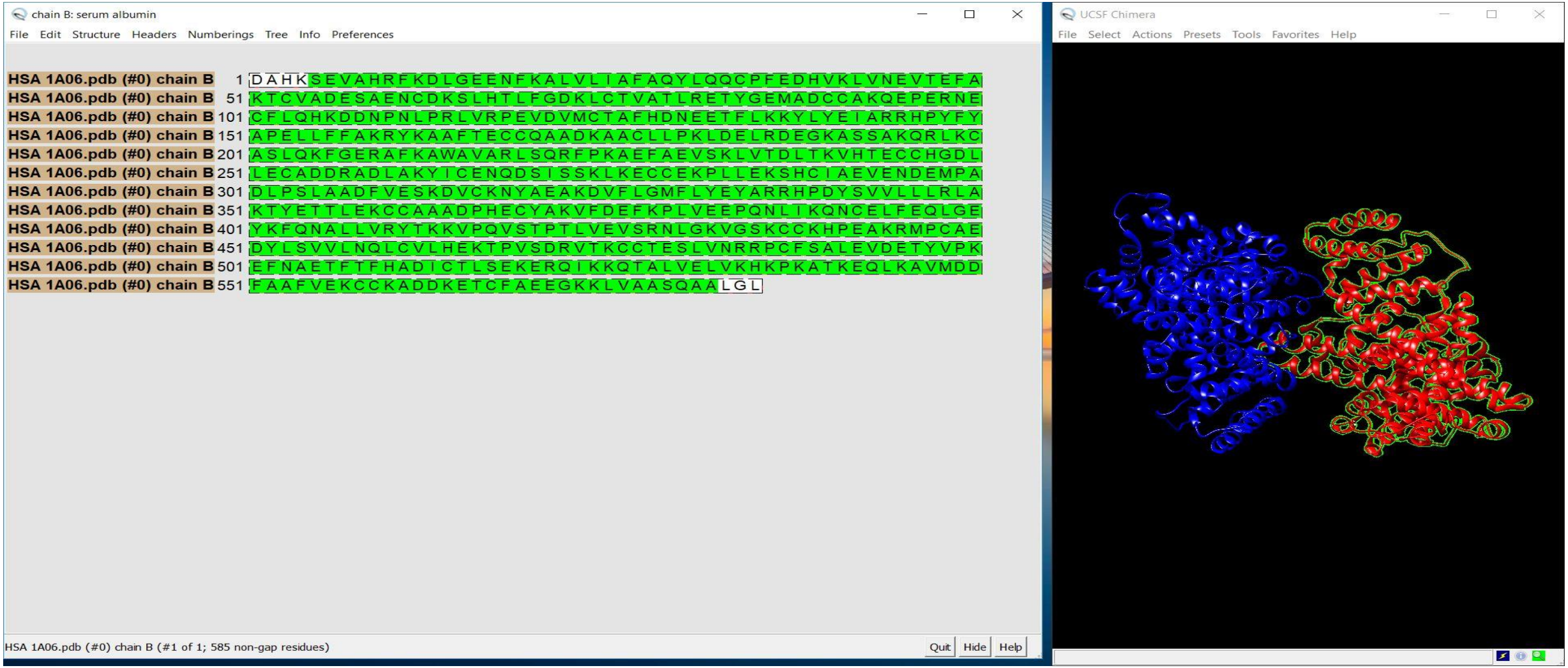
It’s a protein used for transporting hormones in general which are fat soluble hence can be used for many drug delivery studies.



Protein : Human serum albumin (HSA) -seq1-CA



Protein : Human serum albumin (HSA) -seq2-CB



Ligand : Flavin adenine dinucleotide (FAD)

It is a flavoprotein which is a protein that consists of flavin moiety (tricyclic hetrocycle isoalloxazine).

The vitamin riboflavin is the main source for FAD which is vitamin commonly known as vitaminB2 and it is a dietary supplement and it is used to prevent migranes and vitamin B2 deficiency.

But it is also required normally by the body for cellular respiration.

Medical uses of riboflavin are :

1) Remove’s pathogens from blood mainly from donated blood.

2)Corneal ectasia is a progressive thinning of the cornea and it is applied topically

Ligand : Flavin adenine dinucleotide (FAD)

We know flavin moiety (riboflavin etc.) is often attached with adenosine diphosphate(ADP) to form flavin adenine diphosphate (FAD) .

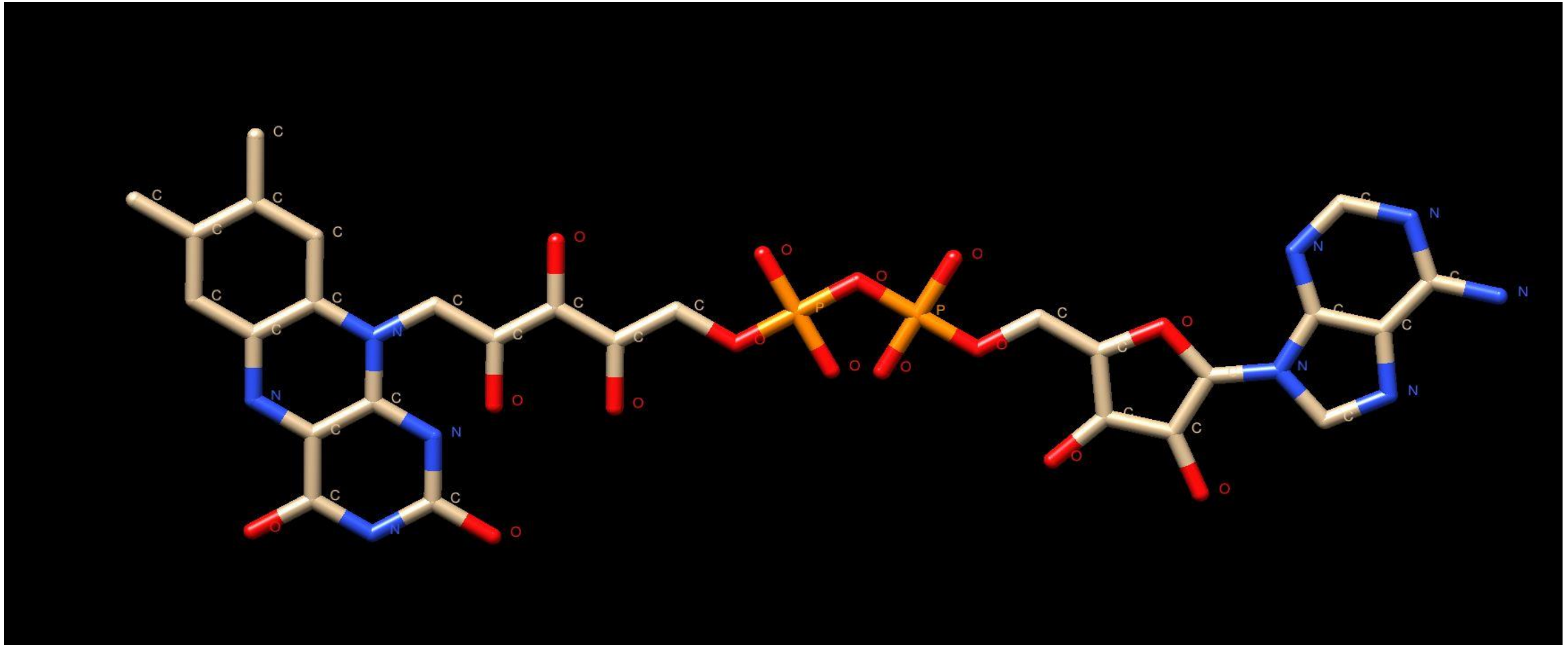
Hence this ligand has ADP an energy carrier and riboflavin aka Vitamin B2 has antimicrobial properties on exposure to UV light A irradiation.

Riboflavin's primary role in the body is supporting your metabolism, helping you access energy from the nutrients that make up your diet. Vitamin B-2 helps your body break down the three macronutrients -- protein, carbohydrate and fat. Riboflavin, in the form of FAD, helps your body break down fats and carbohydrates into fuel by contributing to the electron transport chain, a series of chemical reactions that give off usable energy for your cells.

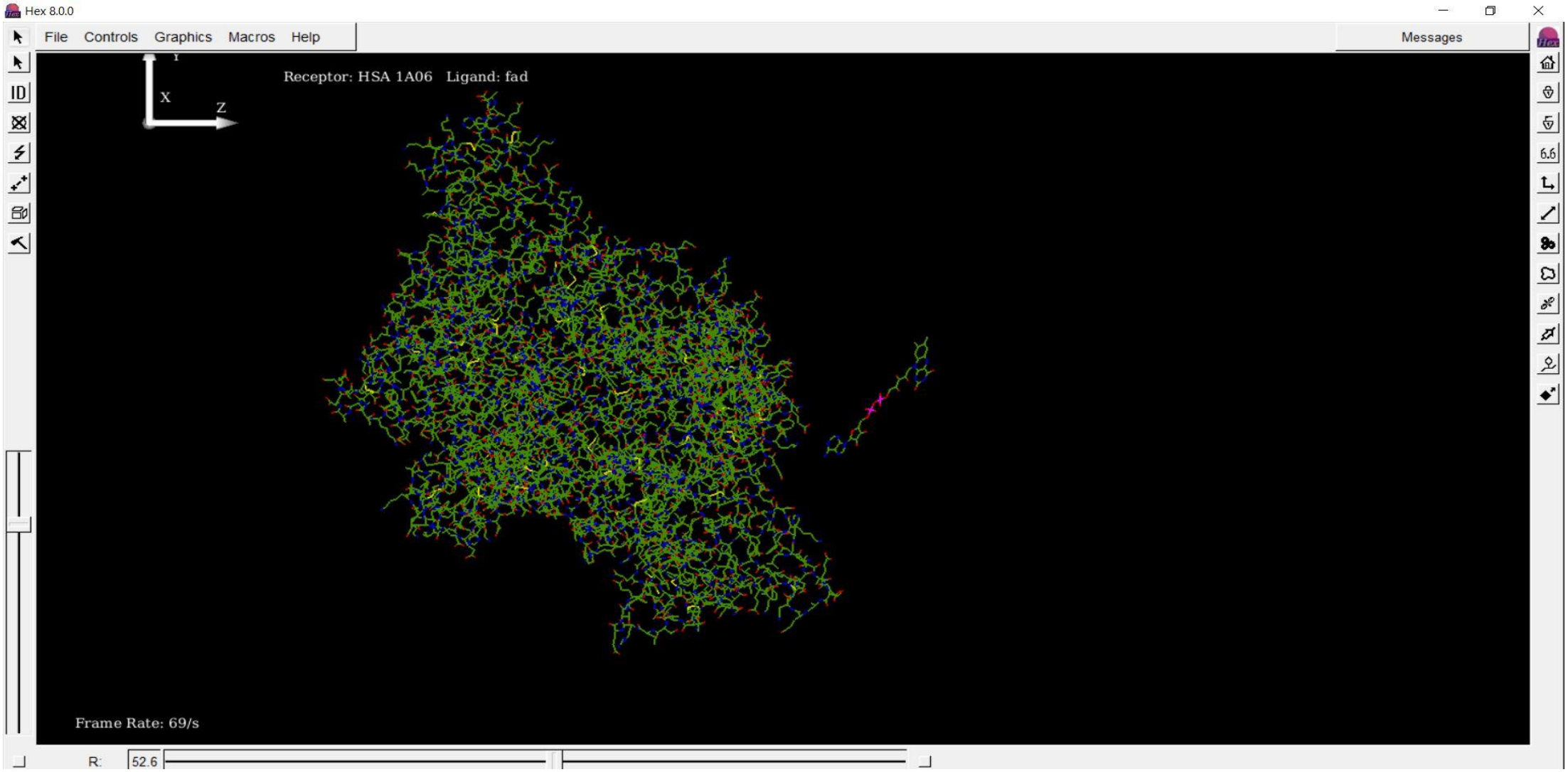
Riboflavin activates the protein cytochrome P450, an enzyme responsible for metabolizing several drugs, including several types of painkillers, antidepressants and anti-epileptic drugs. Failure to consume enough riboflavin might interfere with your body's ability to metabolize pharmaceuticals, potentially altering its response to treatment.

Hence ,it can be used for several drug delivery studies.

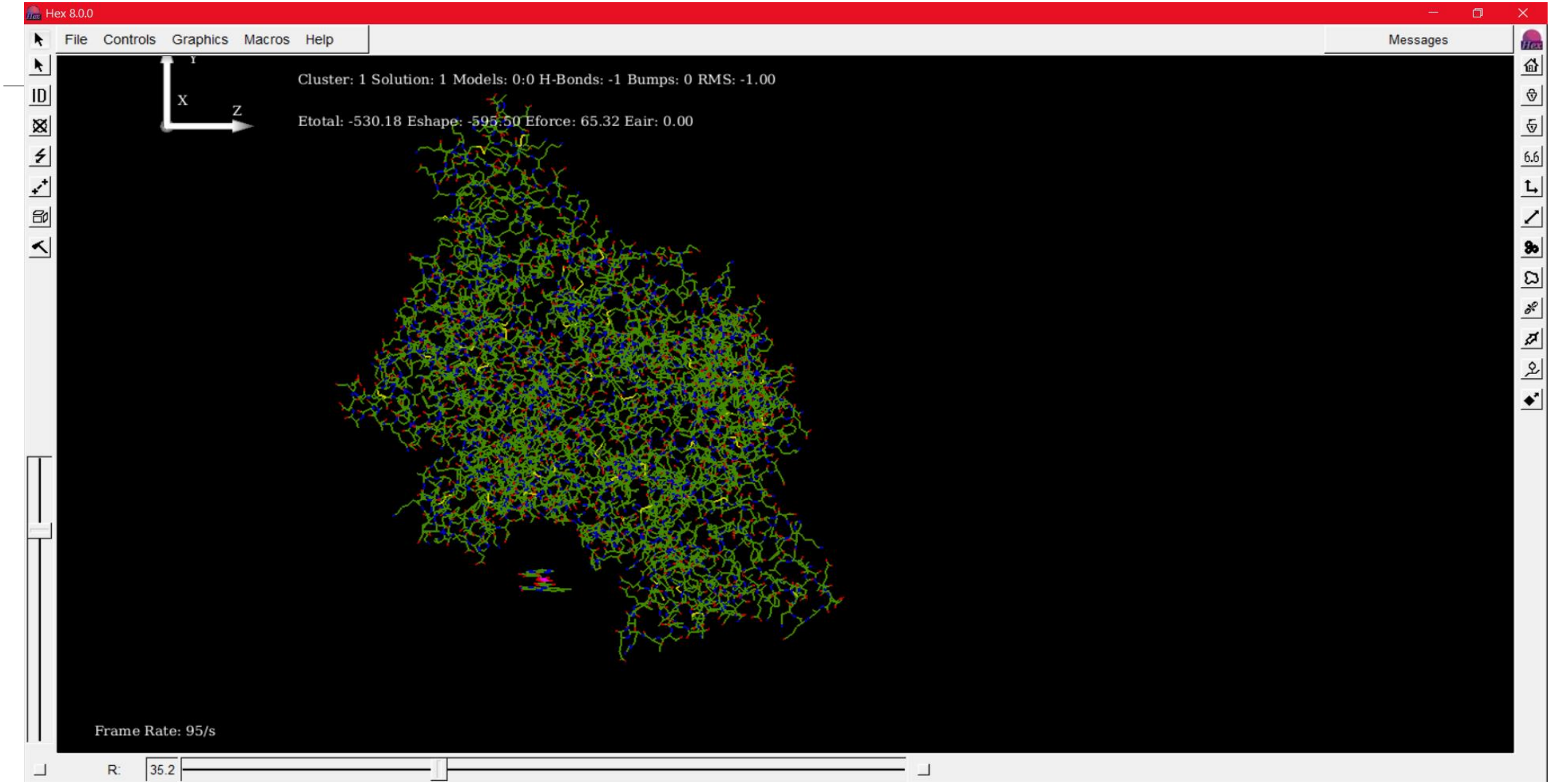
Ligand : Flavin adenine dinucleotide (FAD)



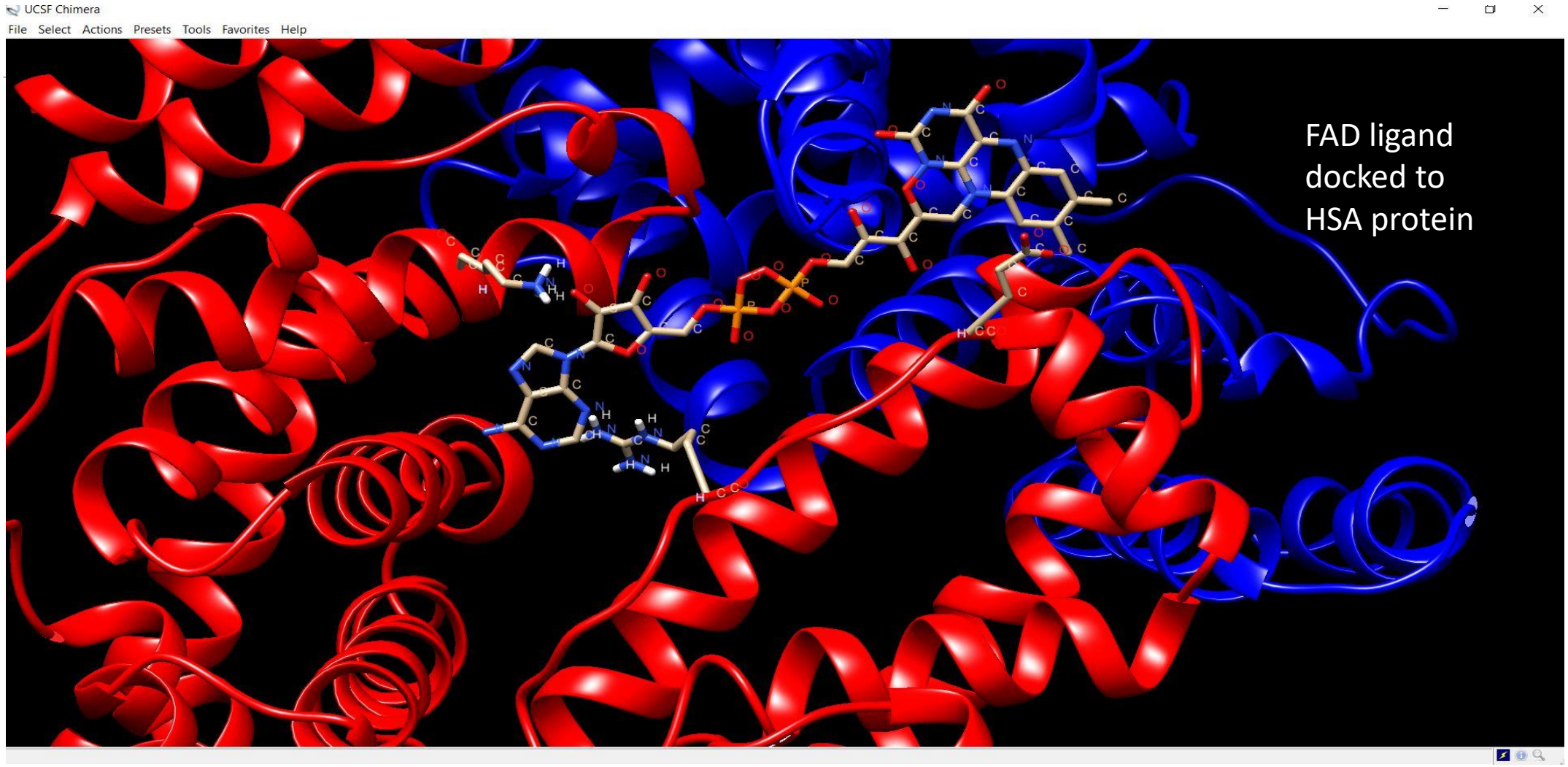
HEX SOFTWARE : BEFORE DOCKING HSA AND FAD :



HEX SOFTWARE : AFTER DOCKING HSA AND FAD



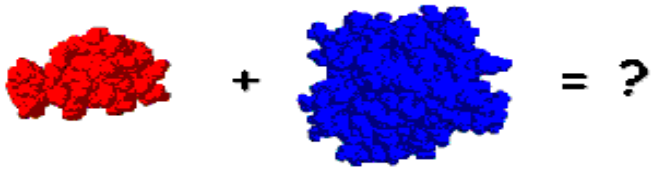
USING UCSF CHIMERA : Viewing docked structure



RESULT OF DOCKING USING HEX

Clst	Soln	Models	Etotal	Eshape	Eforce	Eair	Bmp	RMS
1	1	000:000	-530.2	-595.5	65.3	0.0	0	-1.00

PATCHDOCK



Molecular Docking Algorithm Based on Shape Complementarity Principles

[About PatchDock] [Web Server] [Download] [Help] [FAQ] [References]

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail
HSA1A06.pdb	fad.pdb	Default	4.0	sathyavenkat99@gmail.com

Solution No	Score	Area	ACE	Transformation
1	9092	1077.00	31.02	-0.04 -0.05 -0.03 18.93 -5.24 25.43
2	8590	1049.70	97.19	2.91 -1.19 -0.45 24.83 22.40 30.47
3	8474	1040.60	157.82	2.88 -0.01 -3.06 34.43 -5.18 25.63
4	8224	1009.70	18.15	1.60 0.69 -1.95 30.03 29.94 20.99
5	8222	1062.50	-230.70	1.15 0.89 0.02 26.14 22.54 1.33
6	8212	1010.40	73.50	-0.00 0.07 3.08 34.56 -12.10 24.90
7	8098	1059.90	-9.48	-0.35 -0.80 1.47 43.37 -5.29 21.57
8	8066	1049.20	-46.53	-1.10 -0.43 -1.57 32.09 28.41 14.75
9	8066	957.70	48.11	-1.11 -0.48 1.90 38.37 2.10 15.72
10	8044	1069.10	-68.52	0.58 0.84 -1.92 53.07 6.73 12.49
11	8024	947.00	42.30	3.00 0.48 -0.35 31.68 -9.16 25.21
12	8016	977.80	97.83	-0.22 0.02 2.49 29.60 -12.00 23.96
13	7972	964.20	98.50	-0.11 -0.15 0.25 18.35 -4.70 24.49
14	7918	1126.90	137.48	-1.70 0.32 0.60 19.78 -13.23 15.16
15	7916	1025.80	49.68	1.57 0.53 -1.40 38.53 -5.75 25.54
16	7904	1022.30	-89.69	0.40 0.74 -1.70 50.87 10.46 8.44
17	7896	976.00	-226.81	1.35 0.69 -1.09 43.21 13.98 7.61
18	7894	993.70	-101.37	2.20 1.11 -2.37 29.17 30.61 22.48
19	7886	965.60	-12.69	-1.40 -1.40 2.32 30.72 19.96 21.58
20	7880	1028.40	118.21	0.80 0.62 -2.28 52.22 5.59 13.65

From using Patchdock the results are :

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail
HSA1A06.pdb	fad.pdb	Default	4.0	sathyavenkat99@gmail.com

Solution No	Score	Area	ACE	Transformation
1	9092	1077.00	31.02	-0.04 -0.05 -0.03 18.93 -5.24 25.43

Geometric shape complementarity score, the solutions are sorted according to this score.

Approximate interface area of the complex.

Atomic contact energy

The transformation is of the ligand molecule (3D orientation)

Significance of Docking in this project :

The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized.

Here from the result we obtained -530 as our Etotal that is total electrostatic and vanderwaals interaction in the protein and ligand .This value signifies the ligand and protein’s highly bounded or docked region by various electrostatic forces.

Now we can use this Ligand FAD docked to Protein HSA for direct drug based deliveries as FAD helps our body break down fats and carbohydrates into fuel for ETC (Electron transfer chain) which is used for providing energy to our cells .

We used multiple docking software's in order to get a more refined result for the protein and ligand structure.

Significance of this project :

As Human serum albumin (HSA) is very abundant and is fat soluble hence it can be easily replicated for drug delivery and as Flavin Adenine Dinucleotide (FAD) comes from riboflavin which is also known as vitamin b2 which is necessary for metabolism and is required for most of our body functioning.

Hence this drug can be used for digestive disorders in case of problem in digestion of carbohydrates or fats etc..

We have many replacements to this which are far more productive but this idea can also be used to relieve from riboflavin or vitaminB2 disorders along with digestive issues at the same time.

As it is both easily present in and required for our body hence none to less side effects can be observed on consumption of this drug (protein-ligand complex).

References :

-> https://en.wikipedia.org/wiki/Flavin_adenine_dinucleotide

-> https://en.wikipedia.org/wiki/Human_serum_albumin

-> http://hex.loria.fr

-> https://en.wikipedia.org/wiki/Riboflavin