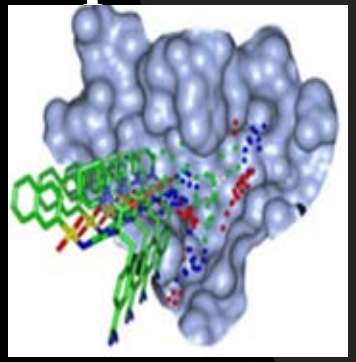
In silico desiging of activator for human IGF2 protein for effective disease therapeutics



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IGF2

Human insulin like growth factor-II (IGF2)

- Insulin like growth factor (IGF2) is one of the protein hormone that share structural similarity to insulin .
- IGF2 belongs to the family IGFs.
- It encoded by IGF2 gene.
- Gene location present on short arm of chromosome 11p15.5
- Sequence length 180 AA.
- IGF2 contain three cell surface receptors IRa, IGF-IR and IGF-IIR.

Function : Human IGF2 acts as regulator of somatic cell growth and cellular proliferation, the major role of IGF2 is as a growth hormone during gestation or foetal development.

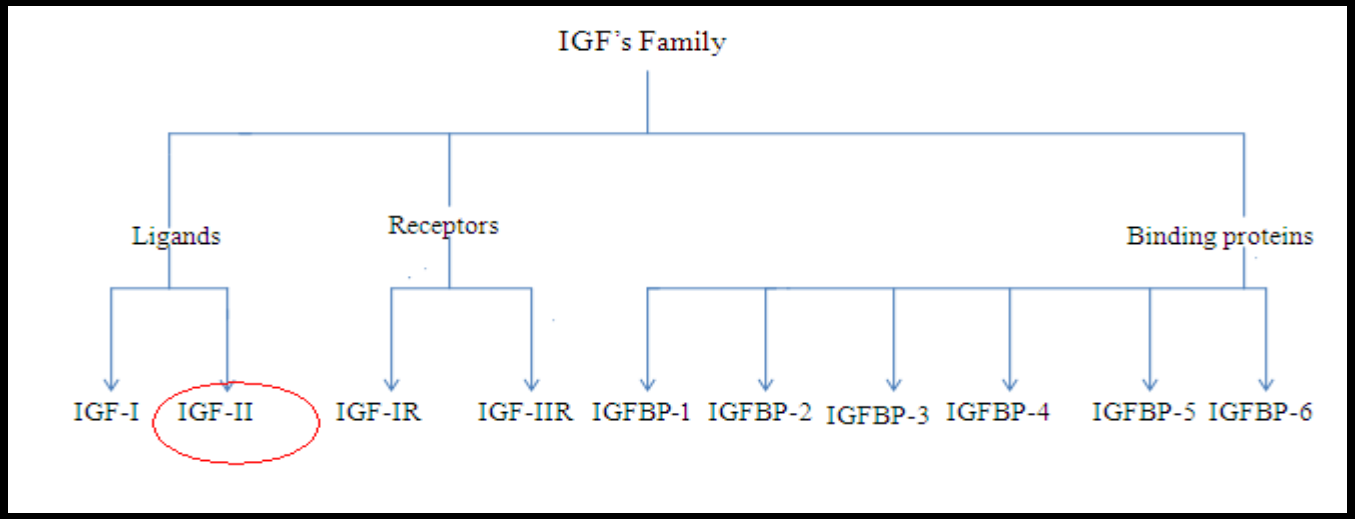
❖The IGFs are part of growth hormone dependent and that mediate many of the anabolic and mitogenic action of growth hormone(GH)

❖ IGFs family or axis contain

Two cell surface receptors(IGF1R, IGF2R)

Two ligands (IGF1, IGF2)

Six high affinity IGF binding protein (IGFBP1 to 6).



❖ The system is involved in the regulation of growth and cellular proliferation in numerous target tissues through endocrine, paracrine and autocrine mechanisms.

Disease relevance of IGF2

- Imprinting of the IGF2 observed in children with renal embryonal neoplasms

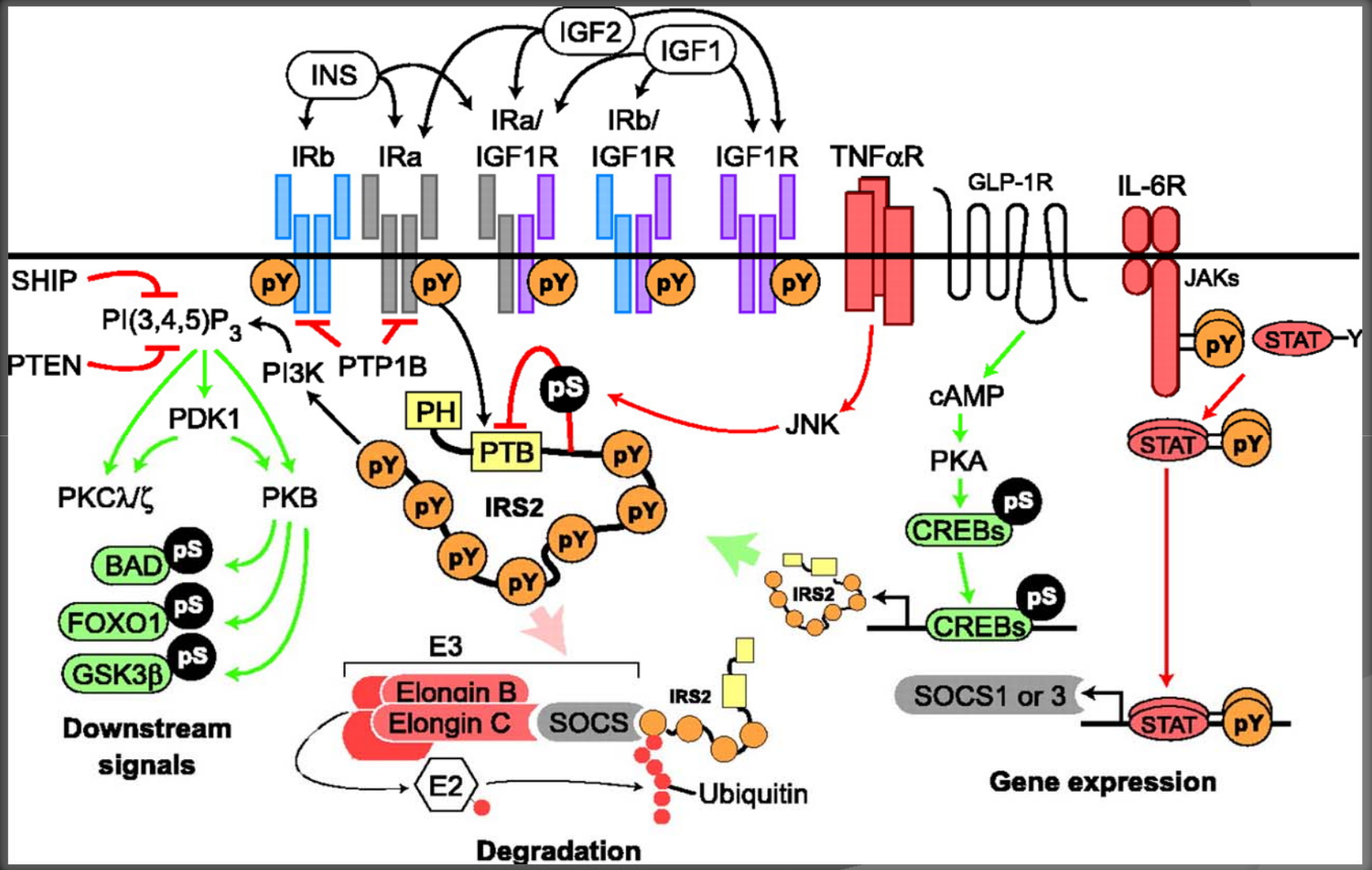
- Loss of imprinting in colorectal cancer and hepatocellullar carcinomas linked to hypomethylation of H19 and IGF2.

- The IGF2-INS-TH genomic region has been implicated in various common disorders including the metabolic syndrome, type 2 diabetes and coronary heart disease.

Type 2 diabetes

- Type 2 diabetes are also called as non insulin dependent diabetes mellitus(NIDDM) or adult onset diabetes .
- Obesity acts as a diabetogenic factor in genetically predisposed individuals by increasing the resistance to the action of insulin , due to decrease in insulin receptors on the insulin responsive cells causes type 2 diabetes.
- The patients of NIDDM may have either normal or even increased insulin levels.
- Over-eating causes increased insulin production but decrease synthesis of insulin receptors, so maintain diet control

Insulin signaling pathway

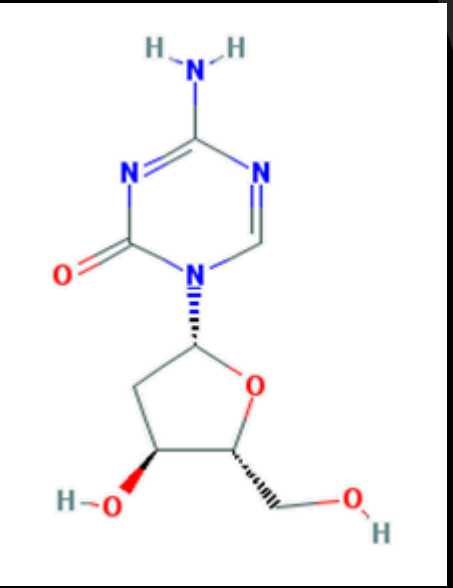


Role of IGF2 in type 2 diabetes

- Dysregulated splicing of exons-11 of insulin alters foetal growth patterns and contributes to causing type 2 diabetes in adults.
- In foetus hypoinsulinemic despite enhanced plasma glucose level due to maternal hyperglycemia, that increase IGF2 expression in the liver and pancreas and IGF2 serum levels are decreased could represent the leading to type 2 diabetes .
- IGF2 serum levels are increased and persistent circulating suppresses developmental apoptosis in the pancreatic islets.
- To treat this disease condition, a drug which activates IGF2 is required.

Existing activator of IGF2

- Name : 5-aza-2 deoxycytidine
- Molecular weight : 282.2 daltons
- Molecular formula : C8H12N4O4
- 5-aza-2'-deoxycytidine(ZCyd) is a drug, taken from literature, increasing the serum levels of IGF2 by changing the DNA methylation and chromatin pattern of IGF2.
- High toxicity of 5aza2'deoxycytidine some silenced genes also expressed like retroviral genes and cancer genes are expressed



5-aza-2 deoxycytidine

AIM

AND

OBJECTIVES

Aim:

In silico designing of activator for human IGF2 protein for effective disease therapeutics.

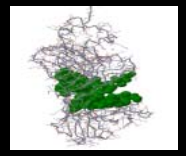
Objectives

- Retrival of IGF2 protein structure
- Prediction of ligand binding sites
- Lead identification and optimization

Molecular docking studies using schrodinger 2011(Maestro v9.2)

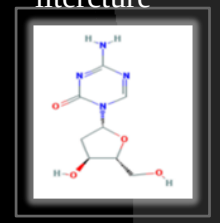
Work flow

Crystal structure



Active sites prediction

Activator from litercture



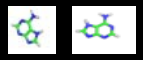
Ligand databases

Docking studies

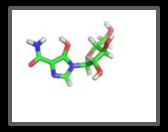
Docking complex

13 leads were obtained

Comprative analysis with literature activator



Four leads



Lead 1

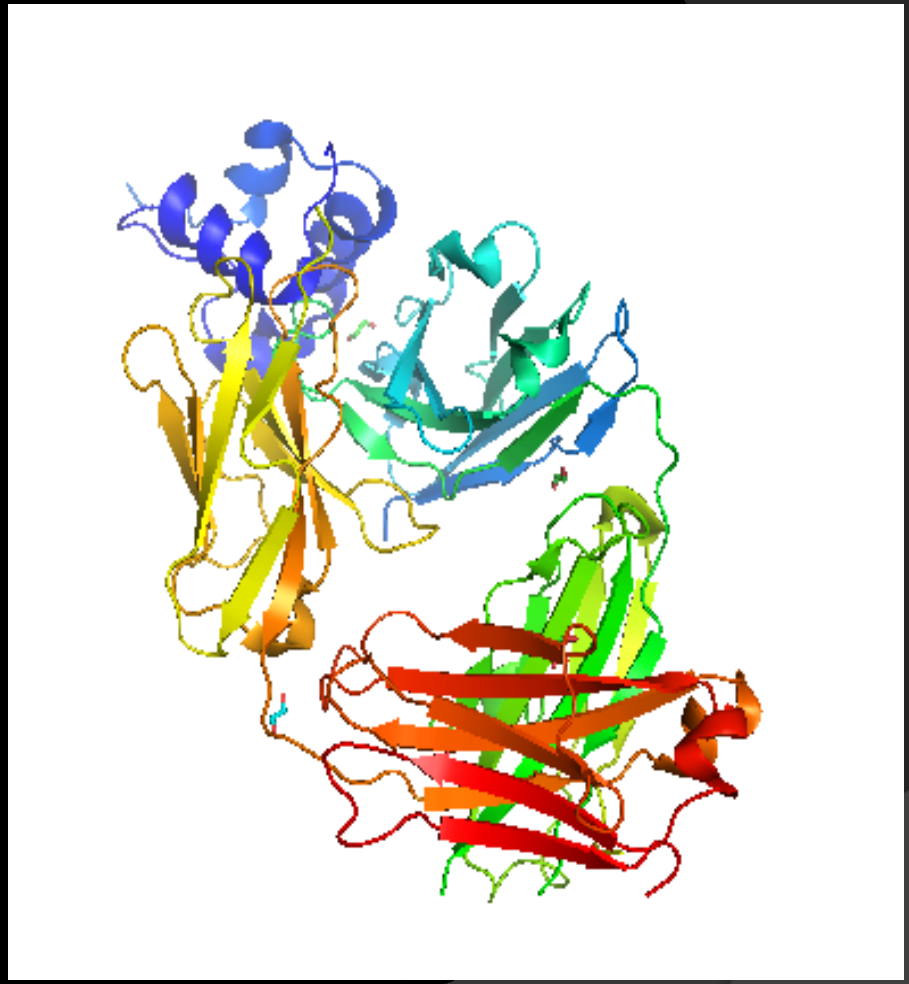
Structure of IGF2

PDB ID : 3KR3

Molecular weight : 57898.88

Length : 67 aminoacids residues

Chains : D,H,L

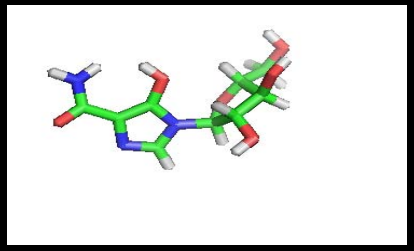


Prediction of ligand binding sites using CASTp

Active site residues in D chain:leu-13,leu-17,iIe-42,val-43,cys-46,leu-56,tyr-59.

Proposed leads

Lead '1'

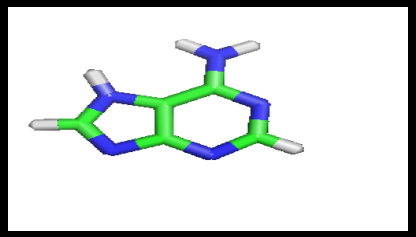


Name : Mizoribine.

Molecular weight : 259.22 Daltons.

XPGscore : -7.18 K.cal/mol.

Lead ' 2'

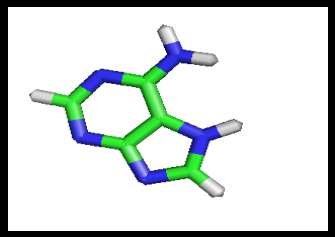


Name : 9H-purin-6-amine.

Molecular weight: 135.13Daltons.

XPGscore : -4.88 K.cal/mol.

Lead '3'

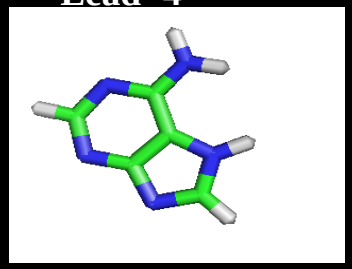


Name :9H-purin-6-amine compound with dichloroplatinum.

Molecular weight : 206.03 Daltons..

XPGscor : -4.88K.cal/mol.

Lead '4'

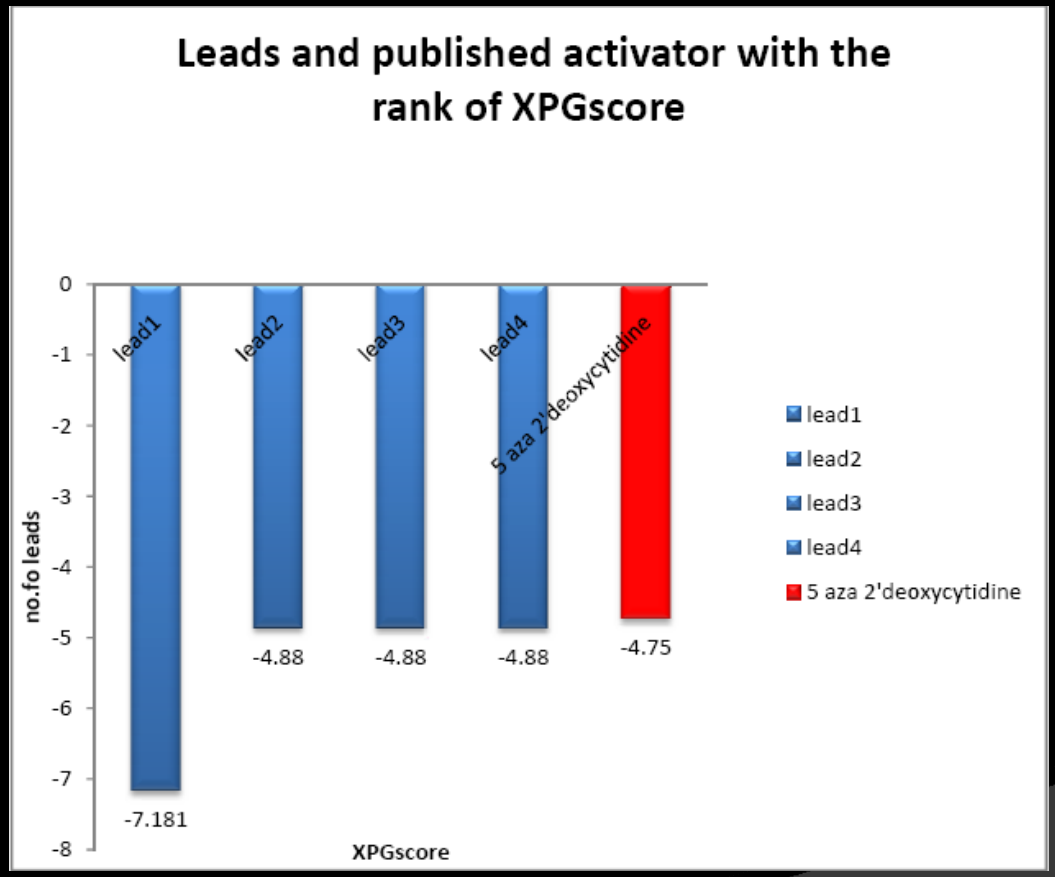


Name : 9H-purin-6-amine compound with aziridine.

Molecular weight : 178.2 Daltons.

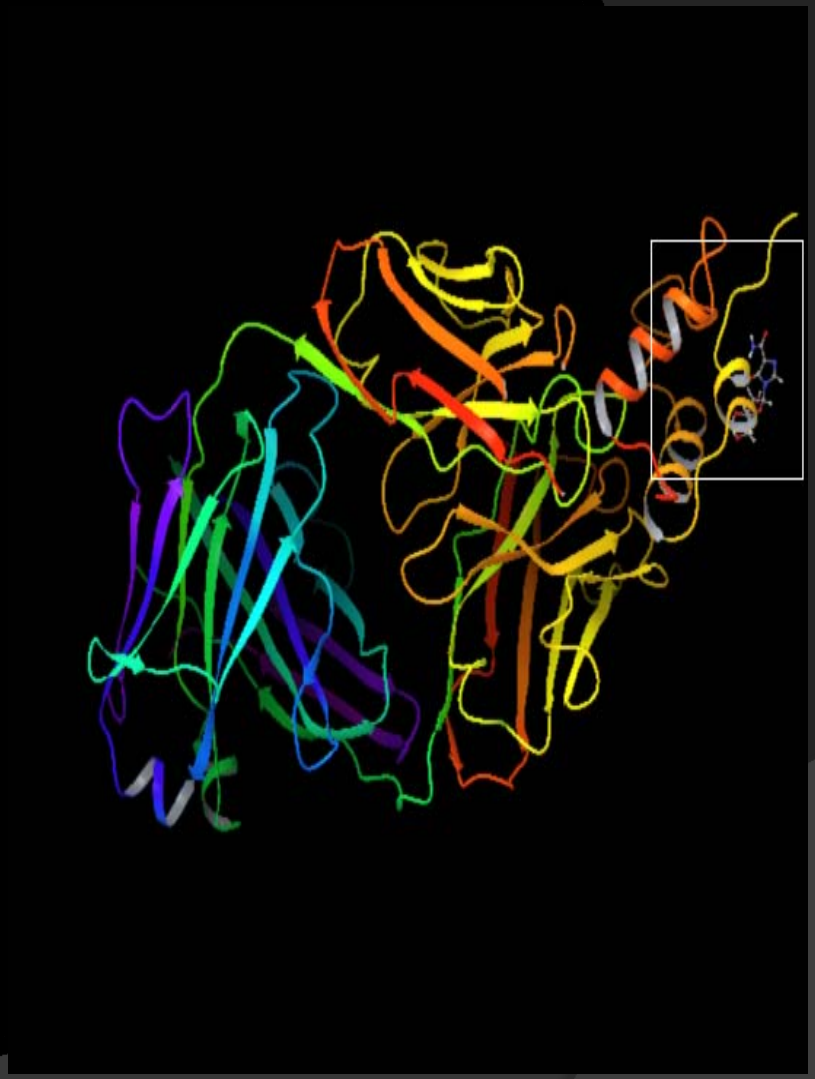
XPGscore : -4.88 K.cal/mol.

Evaluation of the Docking scores



Docking of lead 1 with IGF2

- The four leads bind at the same unique binding pocket of IGF2 protein.



Human IGF2 forming hydrogen bonds with Lead ‘1’

- Three hydrogen bonds were formed stabilizing the protein – lead complex.

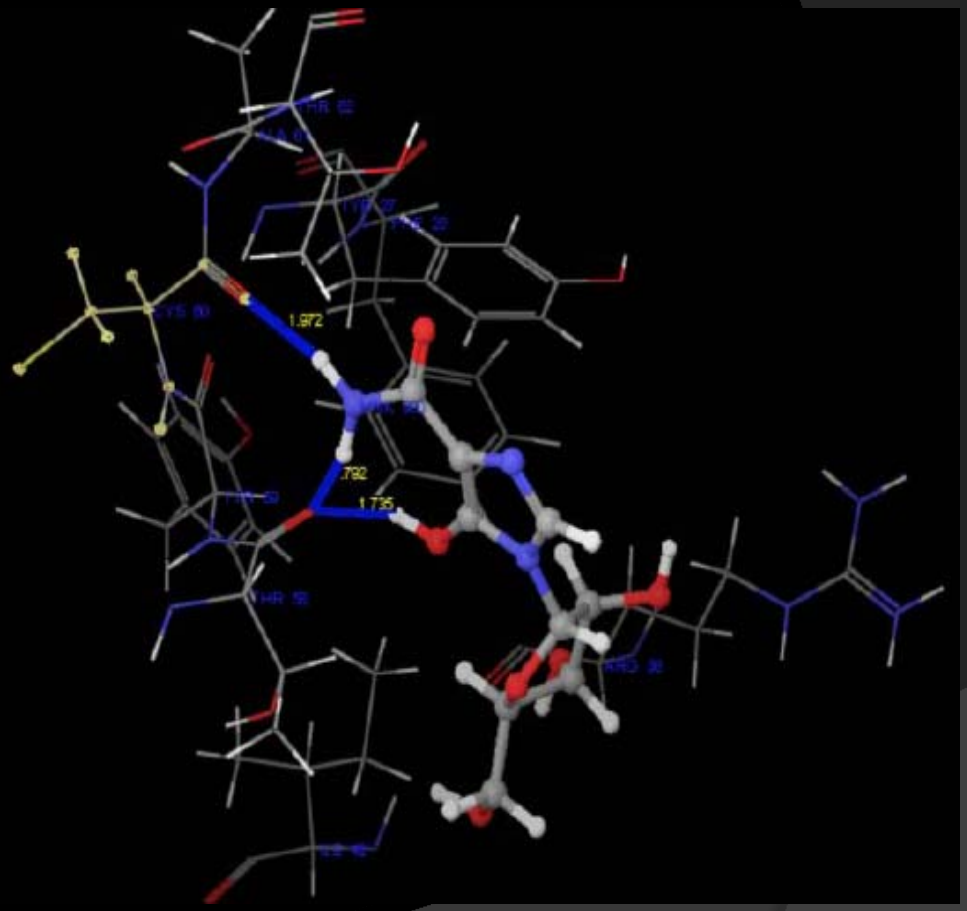
- 2 Hydrogen bonds at Thr-58

  1st hydrogen bond length-1.735

  2nd hydrogen bond length-1.792

- 1 Hydrogen bond at cys-60

  Hydrogen bond length-1.972



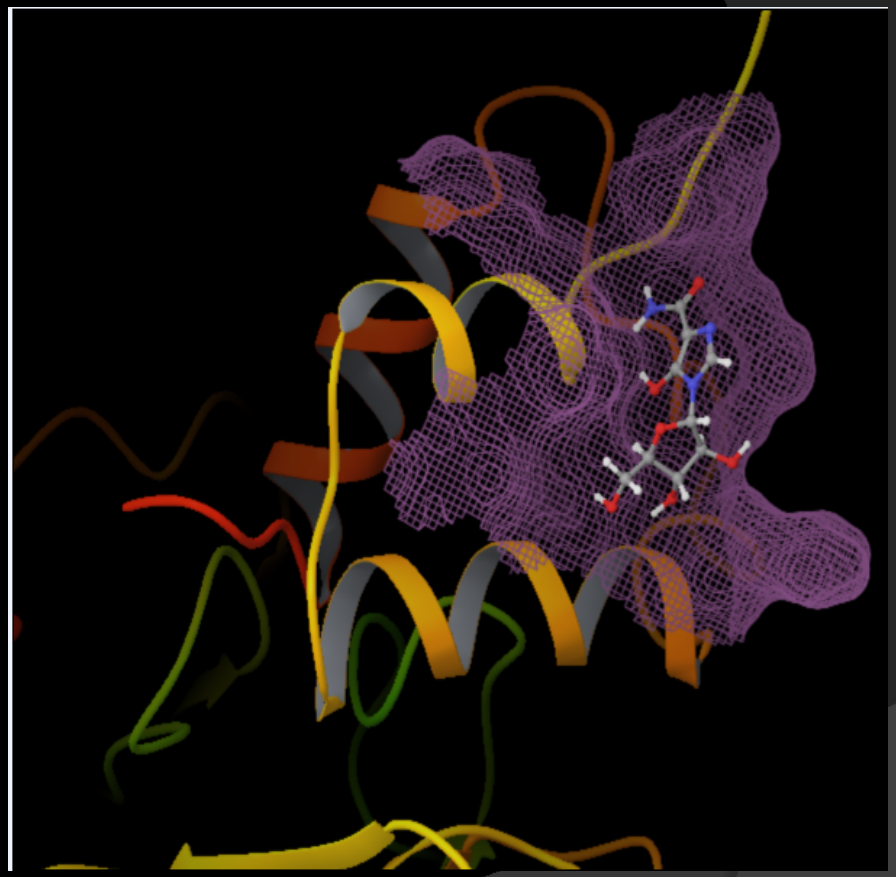
Van der Waal interactions between lead1 molecule and protein IGF2

Ala-61, Cys-60,

Thr-58, Tyr-59,

Phe-28, Tye-27,

Ile-42, Arg-38.



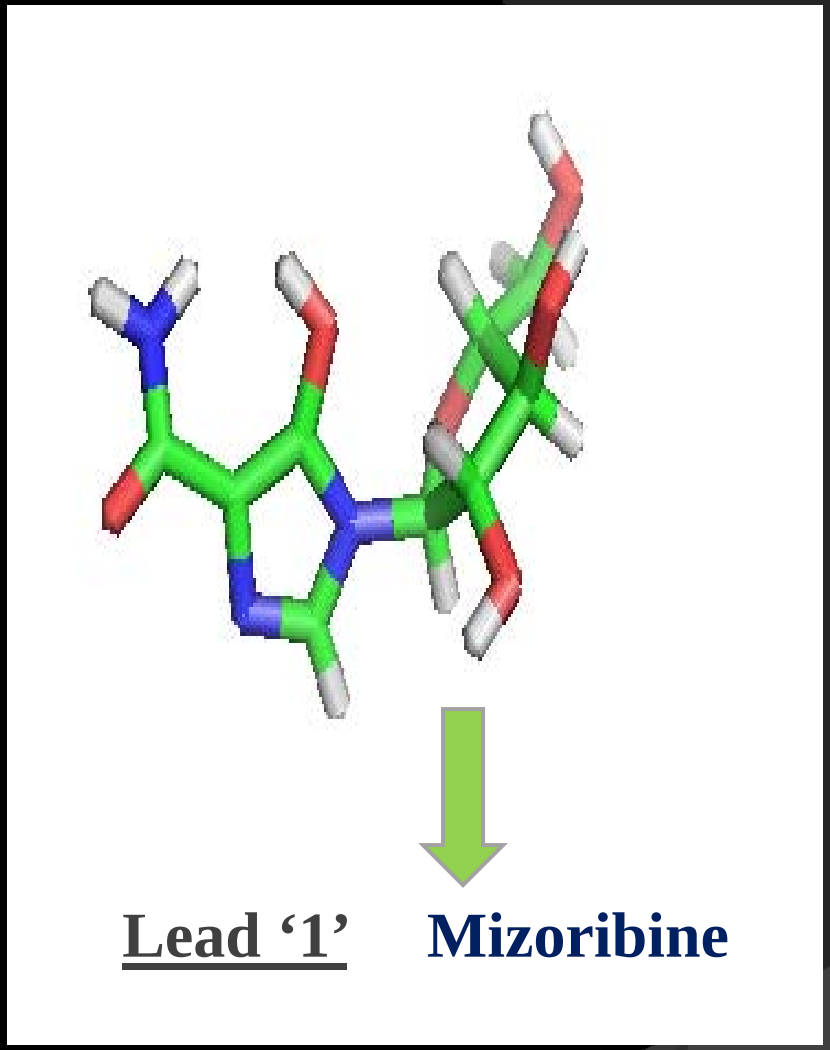
Lead1

Name : Mizoribine

Molecular weight : 259.22 Daltons.

XPGscore : -7.18 K.cal/mol

- Lead ‘1’ activates the activity of human IGF2 in disease conditions than the existing activator.



Lead ‘1’ **Mizoribine**

conclusion

Conclusion

- IGF2 is as a growth hormone during gestation or foetal development.
- Low circulating conceration of IGF-II is associated with an increased risk of type 2 diabetes and cadriovascular diseases
- Docking and scoring studies using schrodinger software, desigened a lead molecules for increasing IGF-II levels.
- The four leads reported in the present study have good binding affinity towards human IGF2.
- However, Lead ‘1’ (mizoribine) with lowest XP G score and good binding orientation with the important binding site residues is suggested as best lead for designing potential activator.

Acknowledgement

- **I express my deep sense of gratitude to the honorable Dr. A. Umamaheswari, Coordinator of BIF & Head of the Department, Bioinformatics, SVIMS, Tirupati for her able guidance and valuable suggestions.**

- **I am thankful to DBT, ministry of science and technology, Govt. of India for providing all the necessary facilities to carry out the project work.**

THANK YOU