Exploring NAG active site of human CD59 towards discovery of novel activators for treatment of diabetes and atherosclerosis

Presented by

C. LAKSHMI NARAYANA RAO

M.Sc., Bioinformatics

Guide

Dr. A. UMAMAHESWARI

Associate Professor & Head

Department of Bioinformatics

Coordinator of BIF sponsored by DBT Govt. of India

INTRODUCTION

DIABETES

- Diabetes (diabetes mellitus) is a metabolic disorder.

- Mechanism of diabetes is, eaten food is broken down into glucose, glucose is a form of sugar in blood. Glucose cannot enter our cells without insulin being present. Insulin makes it possible for our cells to take in the glucose.

- There are three main types of diabetes diseases:

Diabetes Type 1 - Produce no insulin.
Diabetes Type 2 - Don't produce enough insulin or not working properly.
Gestational Diabetes - Develop diabetes during pregnancy.

PROTEIN FUNCTION

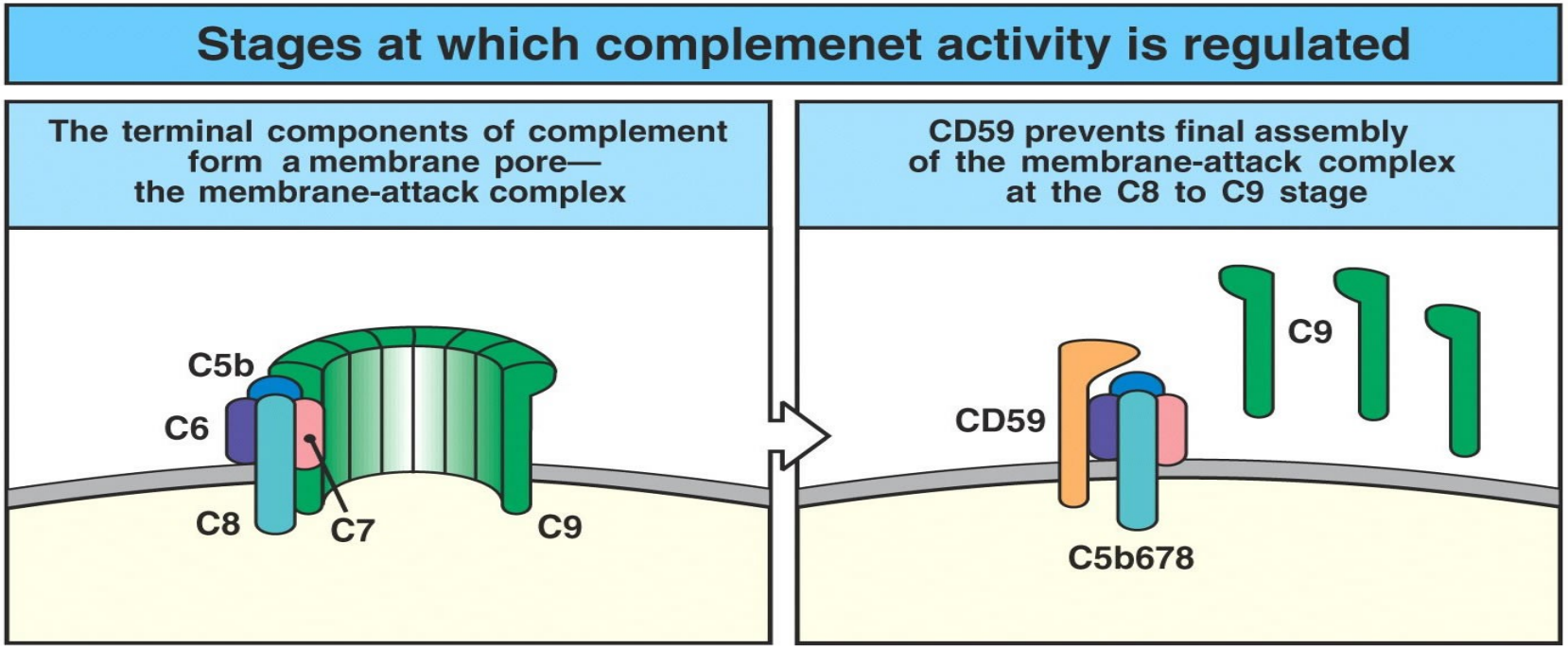
- CD59 expression on peripheral blood leucocytes were down regulated in type-2 diabetes with macrovascular diseases.

- Diabetic macrovascular diseases, such as cerebrovascular diseases, coronary artery diseases and peripheral vascular diseases are mediated by atherosclerosis.

- Activated through classical pathway, alternative pathway and lectin pathway.

- CD59 is a GPI anchored membrane bound that specifically inhibits the formation of the MAC. Complement system play important role in diabetic macro vascular diseases.

Fig. The membrane attack complex structure of human CD59



➢ C5b convertase enzyme and the terminal pathway pore-like membrane attack complex (MAC) formation, which result in cell lysis.

Original article

Decreased expression of complement regulatory proteins, CD55 and CD59, on peripheral blood leucocytes in patients with type 2 diabetes and macrovascular diseases

MA Xi-wen, CHANG Zhi-wen, QIN Ming-zhao, SUN Ying, HUANG Hui-lian and HE Yan

Keywords: *diabetes mellitus, type 2; diabetic angiopathies; CD55; CD59*

Background Macro- and microvascular diseases are the leading cause of morbidity and mortality in diabetic patients, but their mechanisms remain unclear. Recent reports provide evidence that the levels of CD55 and CD59 are decreased in diabetic microvascular diseases. However, very little is known about the levels of CD55 and CD59, the relationship between them and carotid artery intima-media thickness, and the effects of statins on CD55 and CD59 in diabetic macrovascular diseases.

Methods The mean fluorescence intensity (MFI) of CD55 and CD59 expression on peripheral blood leucocyte subsets (lymphocytes, monocytes and neutrophils) was studied using flow cytometry, and carotid artery intima-media thickness was measured using B-mode ultrasonography in 23 healthy subjects (controls), 19 patients with type 2 diabetes (T2DM), and 43 patients with type 2 diabetes and macrovascular diseases (T2DM-M). The patients with T2DM-M were assigned to two subgroups based on whether statins were used: group with statins (n=23) and group without statins (n=20).

- The presence of hCD59 extensively in human tissues, including kidneys and nerves.

- Human CD59 is inactivated by glycation of its K41 residue because it contain a glycation site formed by residues K41-H44 mutations.

- Statin is the drug for the Type-2 diabetes and the macrovascular diseases.

- Statin has some side effects, they are headache, vomiting, diarrhea, rash, rarely liver damage, weakness and muscle pain.

- So that further studies to better drug for than Statin to Type-2 diabetes and macrovascular diseases in humans.

AIM : Exploring NAG active site of human CD59 towards discovery of novel activators for treatment of diabetes and atherosclerosis

OBJECTIVES :

- Annotation of structural and functional aspects of human CD59.
- Prediction of active site residues.
- Lead identification and optimization through computational docking and high throughput virtual screening (HTVS).

MATERIALS AND METHODS

WORK FLOW:

Structure

RCSB PDB PROTEIN DATA BANK

Lead Identification

Ligand.info

- Harvard ChemBank - 2,344 records
- E-MSD ChemPDB - 4,009 records
- KEGG Ligand - 10,005 records
- Anti-HIV NCI - 42,689 records
- Druglikeness NCI - 192,323 records
- Unannotated NCI - 15,237 records
- AKos GmbH - 544,391 records
- Asinex Ltd. - 348,276 records

Pathway Analysis

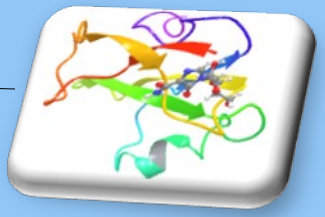
KEGG

Docking Studies

SCHRÖDINGER

(Maestro v9.2)

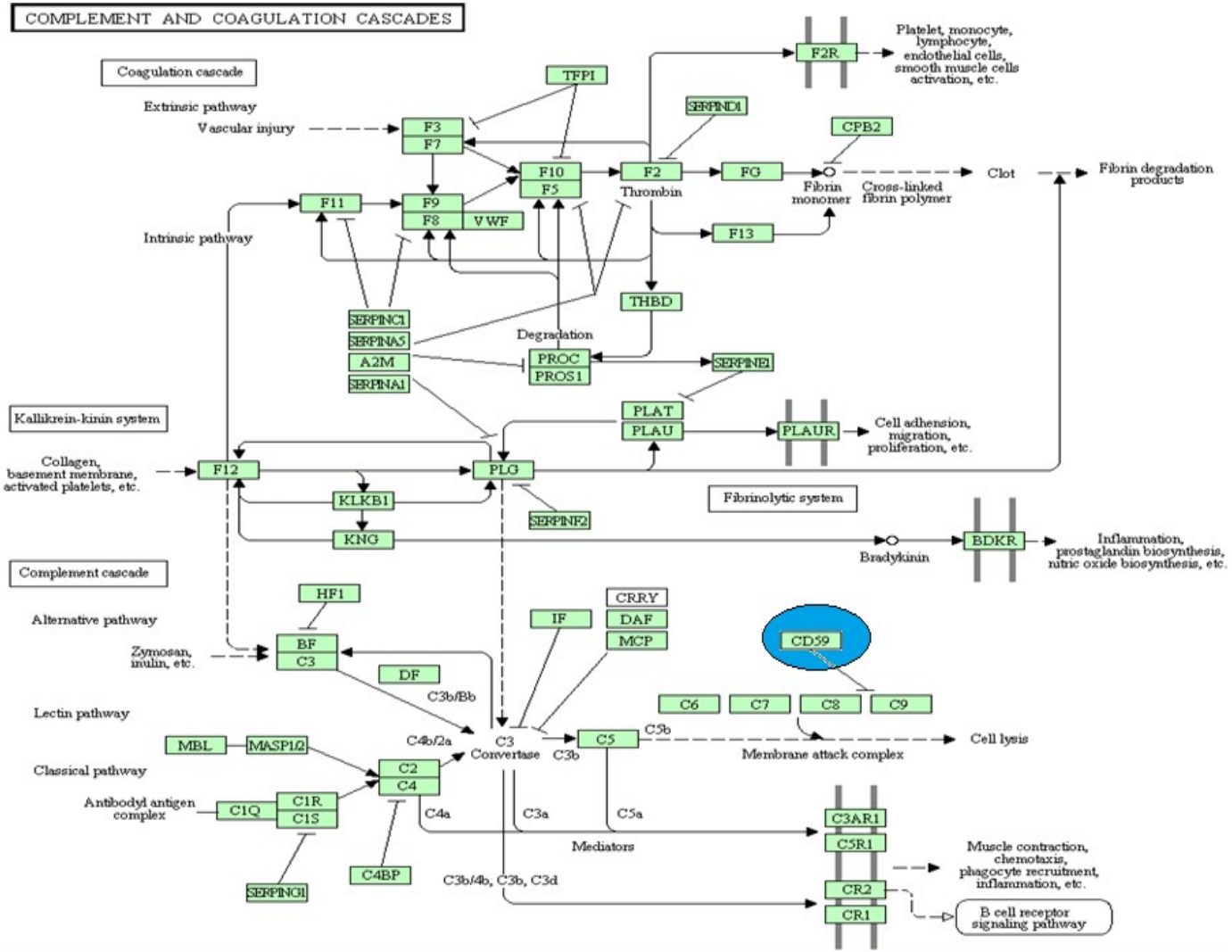
(Virtual Screening)



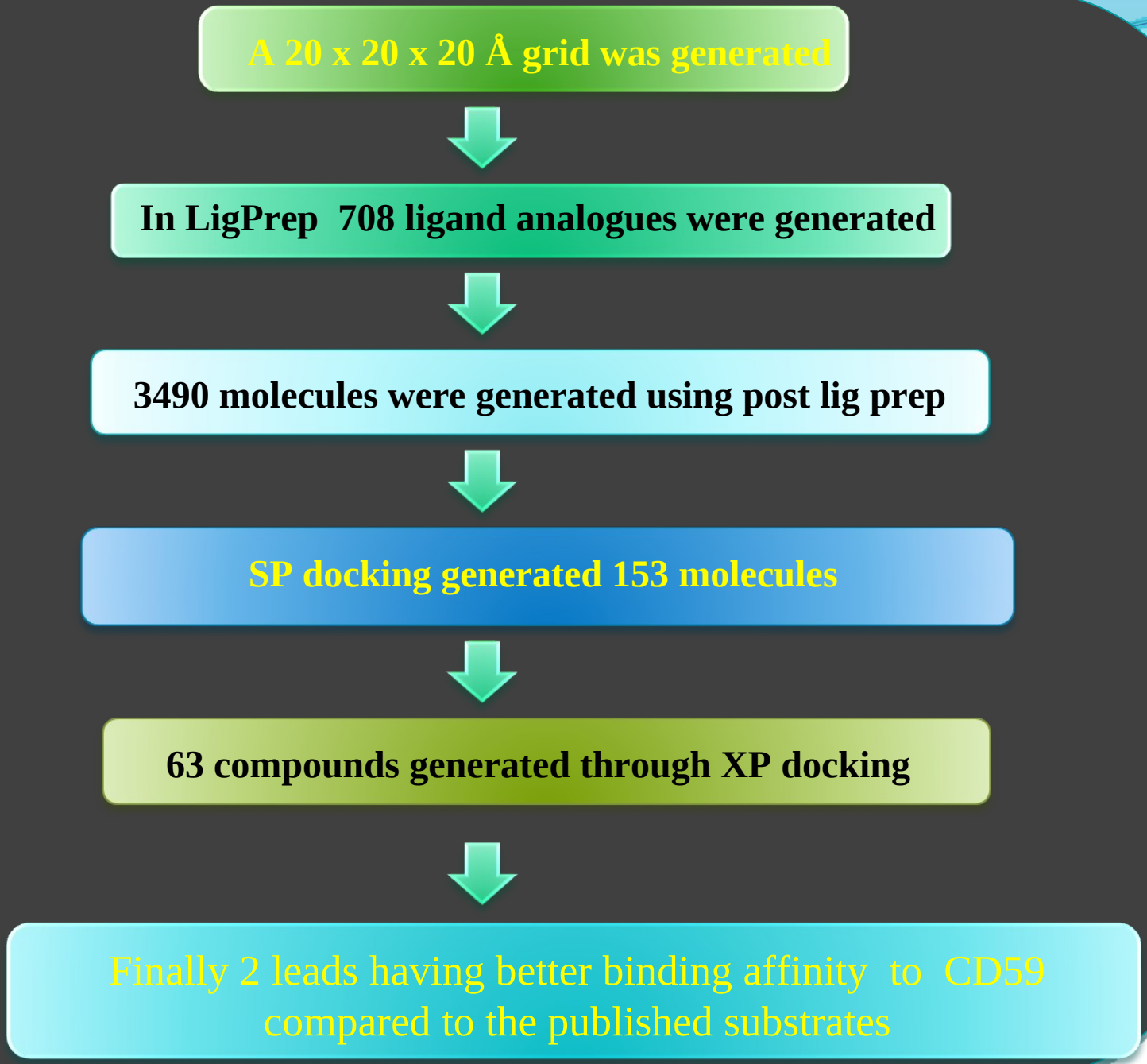
(Lead '1')

RESULTS AND DISCUSSION

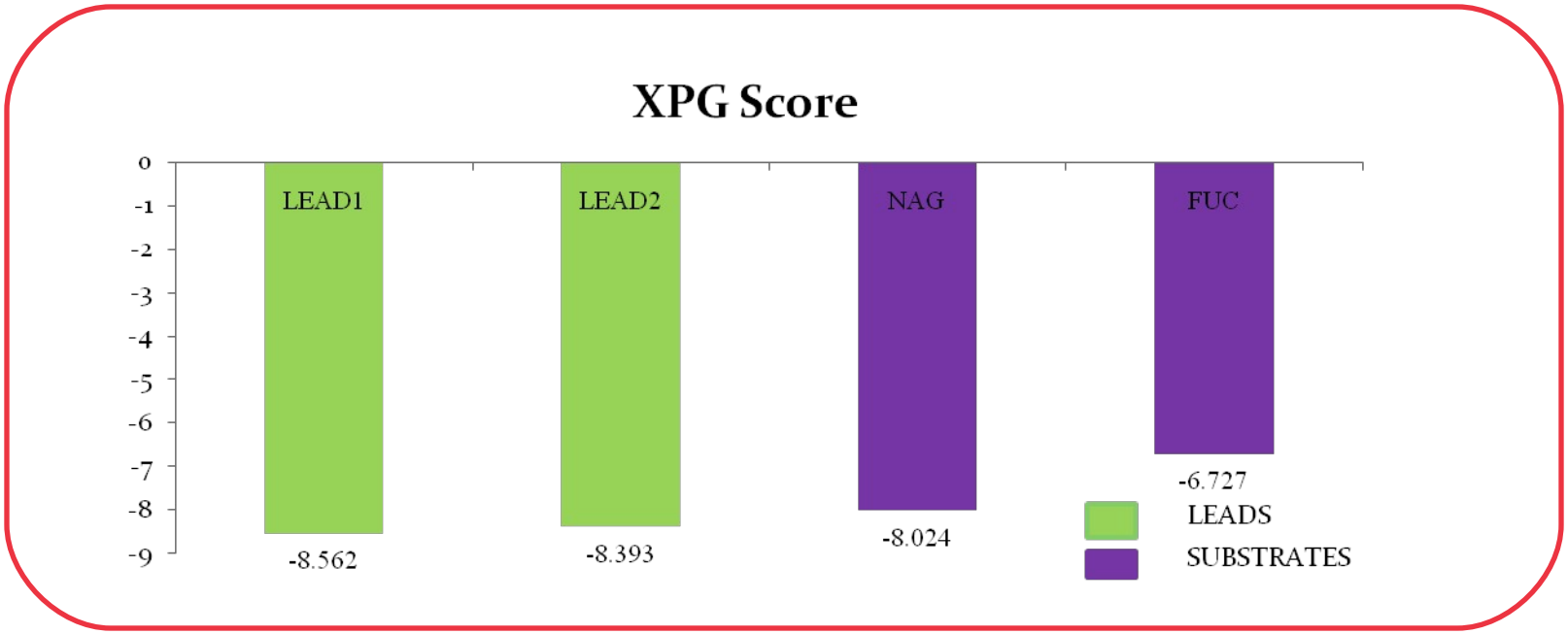
COMPLEMENT AND COAGULATION CASCADES PATHWAY

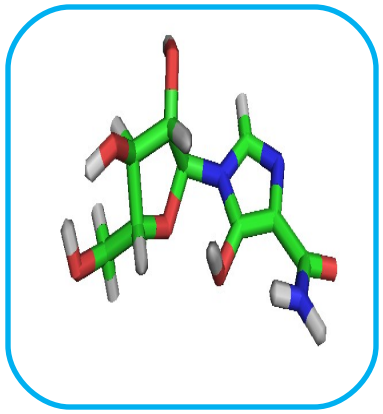


WORKFLOW

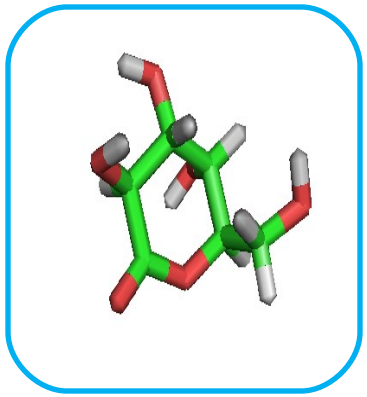


GRAPHICAL REPRESENTATION OF XPG SCORE



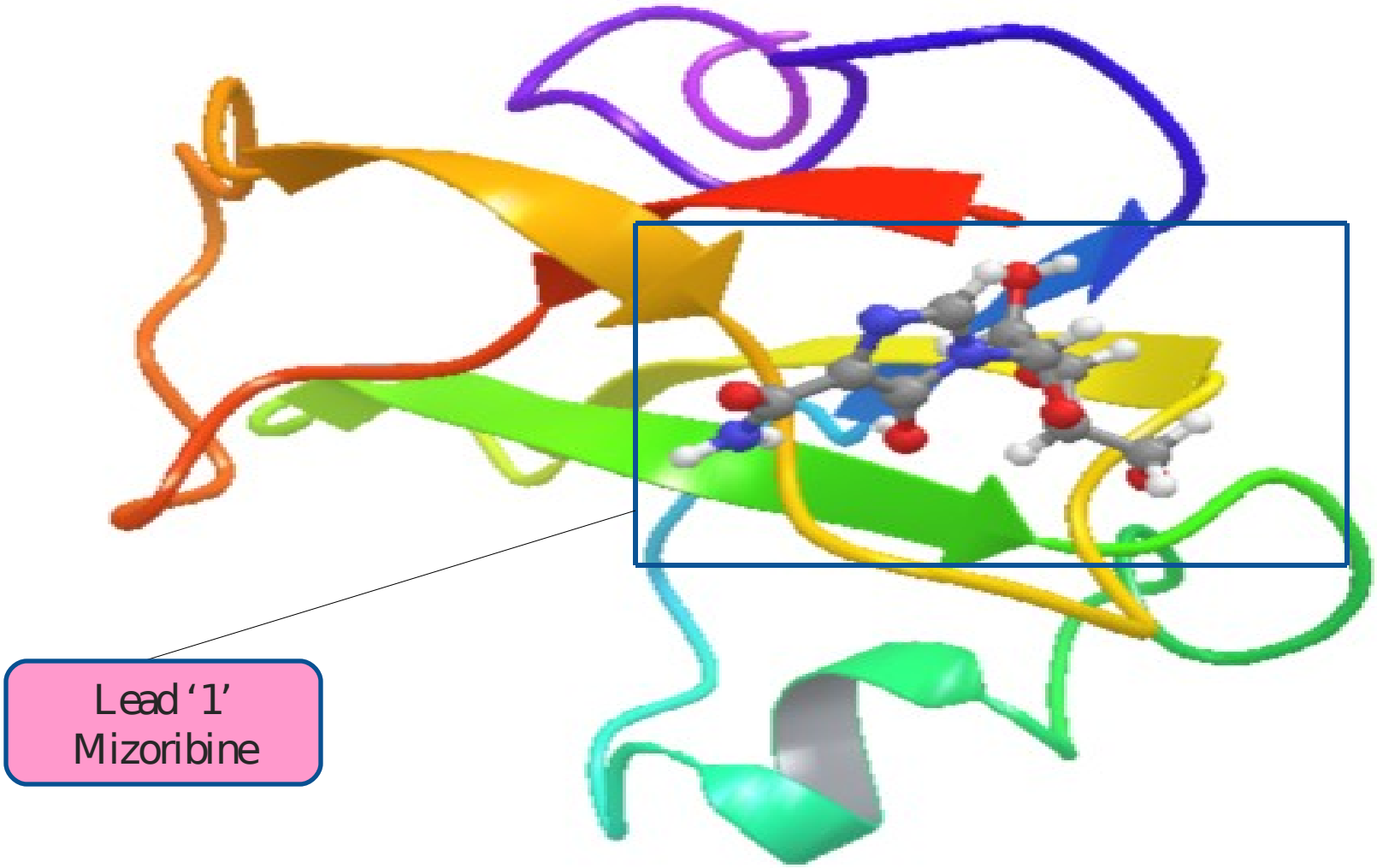


Lead ‘1’

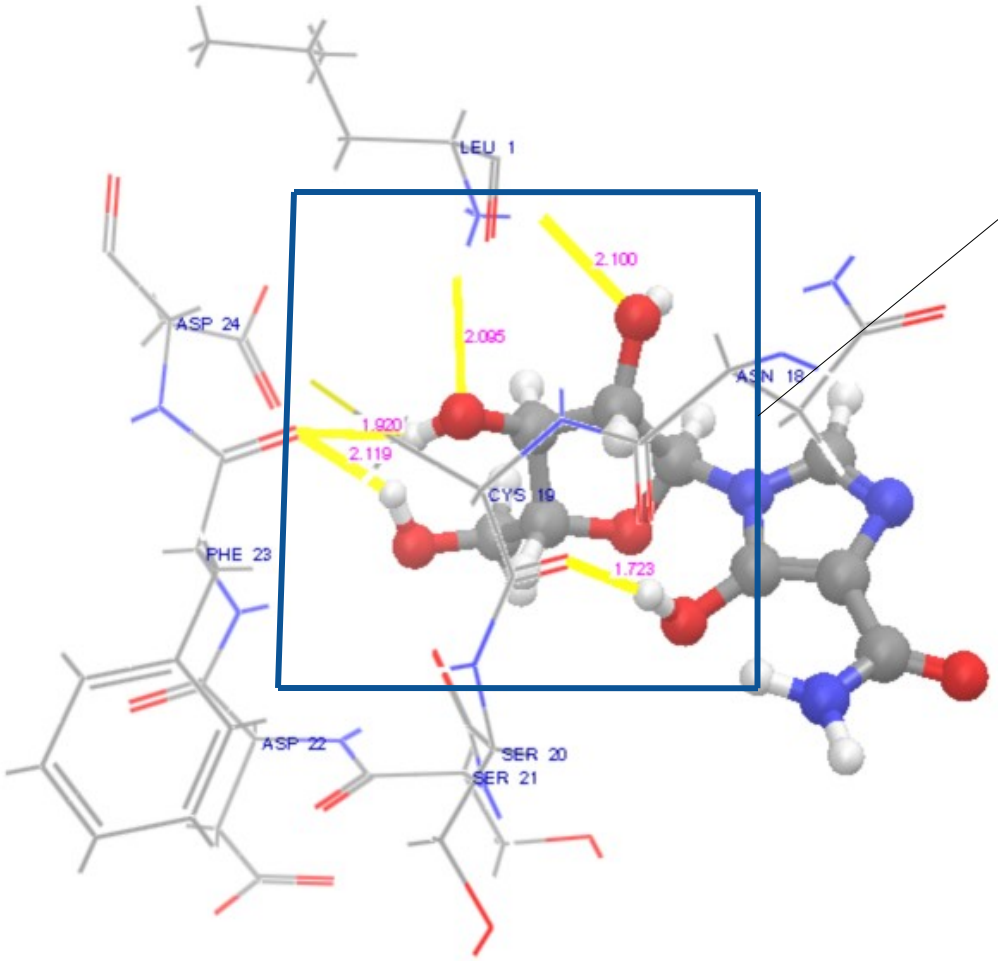


Lead ‘2’

Docking complex of the lead ‘1’ with the human CD59



Hydrogen bond network between lead ‘1’ and human CD59



Four hydrogen Bonds

Gly77, Asn78, Lys97 and Asp208 of CD59 forming hydrogen bonds with Lead ‘1.

Van der Waal Interactions

Leu1, Asn18, Cys19, Ser20, Ser21, Asp22, Phe23 and Asp24.

CONCLUSION

- CD59 low expression in Type-2 diabetes leads to macro-vascular diseases and atherosclerosis in humans.

- Through computer aided drug designing approach Lead'1 act as potential activator for CD59 diabetic therapy.

- Gly77, Asn78, Lys97 and Asp208 of CD59 forming four hydrogen bonds with Lead '1' (mizoribine). Thus lead 1 having good XPG score of -8.562 k. cal/mol.

- Mizoribine have potential in controlling diabetes if synthesized and tested in animal model.

THANK YOU