Docking studies to explore novel lead molecules for human spleen tyrosine kinase involved in chronic lymphocytic leukemia

Naveen kadaari,* Dibyabhaba Pradhan, Muni kumar and Amineni Umamaheswari**

Bioinformatics Centre, Department of Bioinformatics, SVIMS University, Tirupati, PIN 517507.
* Presenting Author; ** Corresponding Author; Email: svims.btisnet@nic.in

Introduction

1.B-cell chronic lymphocytic leukemia (CLL) is the most prevalent B-cell malignancy in adults.

2.Spleen tyrosine kinase (SYK) plays a pivotal role for B-lymphocyte development and maturation in B-cell receptor (BCR) signaling pathway

3.SYK is activated by conserved tyrosine residues sequential phosphorylation. SYK phosphorylates several downstream signaling elements, such as BLNK, Vav, Btk, phospholipase Cγ2 (PLCγ2), and growth factor receptor binding proteins.

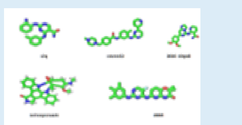
4.Designing SYK inhibitors would reduce phosphorylation of SYK downstream targets and induced apoptosis in primary chronic lymphocytic leukemia cells hence represents a potential therapeutic target for CLL.

5. **The present study is directed towards finding novel inhibitors of SYK through ligand based virtual screening.**

Materials &methods

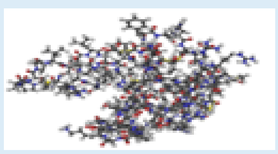
Structure retrieval

SYK protein structure



Five published inhibitors

Ligand.info



1957 structural analogs

Schrödinger Software
Virtual screening (HTVS, SP and XP)

Fifteen lead molecules

Two potential inhibitors
(Comparative analysis with published inhibitors)

Results & discussion

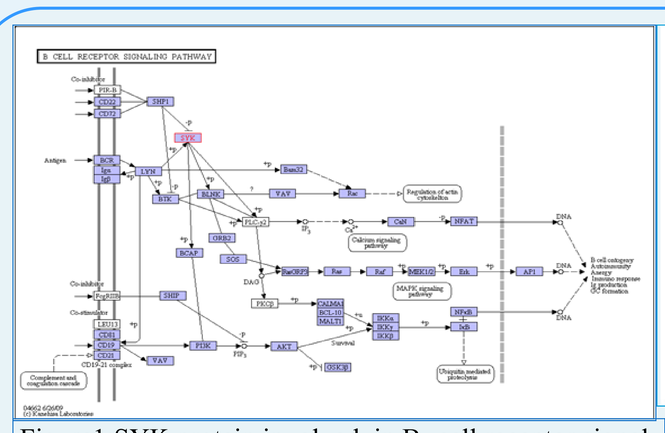


Figure1:SYK protein involved in B- cell receptor signaling Pathway

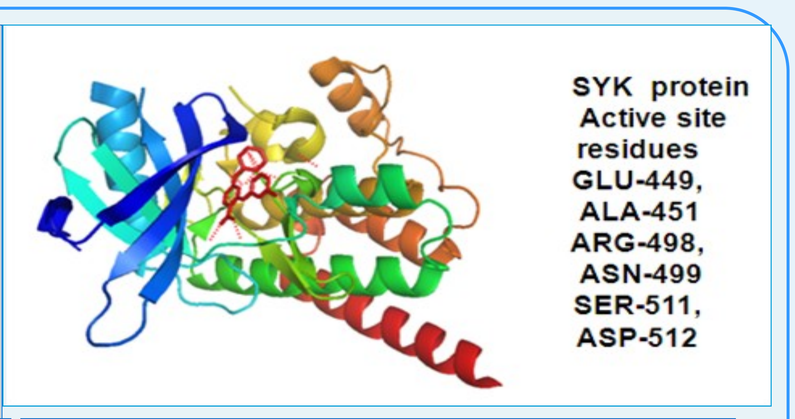


Figure2:Human SYK protein X-ray crystal structure with p5c ligand .

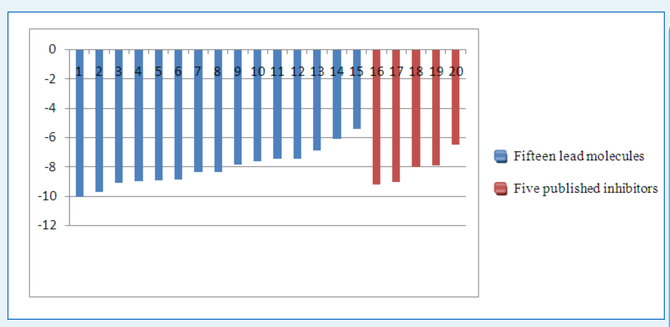
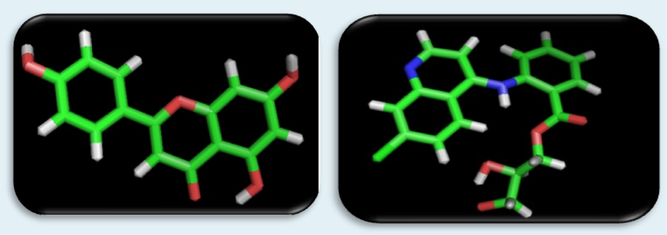


Figure3:Comparison of XP G scores of SYK five published inhibitors along with fifteen lead molecules



Apigenin

Glafenine

Figure 4:Best two leads

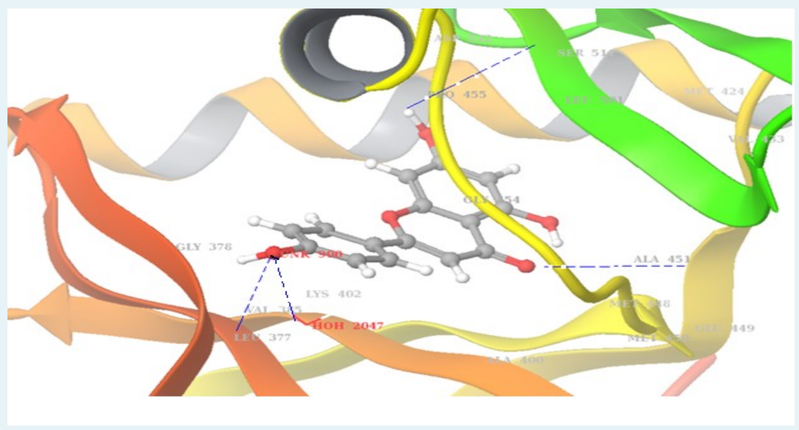


Figure 5:Lead '1' molecule (apigenin) forming 4 Hydrogen bonds with SYK protein residues and least docking score-(-10.05 kcal/mol). Hydrogen bonds are Leu-377,Ala-451,Asp-512W-2047

1.Apigenin (4,5,7-trihydroxyflavone), a common dietary flavonoid abundantly present in fruits and vegetables, shows promising biological effects such as prevention and therapy of prostate cancer, suppression of tumor genesis and angiogenesis in melanoma1and breast, skin, and colon carcinomas.

2.Glafenine -Chemical name: Benzoic acid, 2-((7-chloro4quinlinyamino),2,3dihydroxypropylester. An anthranilic acid derivative with analgesic properties used for the relief of all types of pain.

conclusion

Fifteen lead molecules with good binding affinity to SYK were identified and compared with binding affinities and orientations of five published inhibitors.

Apigenin (-10.05 Kcal/mol) and Glafenine (-9.72 Kcal/mol) endeavored better binding affinities, hydrogen bonding network and Van der Waal interactions with active site residues compared to published inhibitors.Thus, Apigenin and Glafenine would be valuable for designing novel inhibitors against CLL, if synthesized and tested *in vitro* and *in vivo*.

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