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QSAR AND PHARMACOPHORE MODELING BASED DRUG DESIGNING FOR SPLEEN TYROSINE KINASE (SYK) PROTEIN FOR HUMAN USING ACCELRYS DISCOVERY STUDIO SOFTWARE IN LINUX SERVER

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Keywords:

Accelrys discovery studio, SYK Protein, Virtual screening, QSAR, Pharmacophore, Docking

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ABSTRACT: From this current research, Syk (spleen tyrosine kinase) protein and gene information is analyzed by different genomics, proteomics tools & databases. One crystal ligand 4DFL was collected from protein data bank (pdb). From different literature review 131 syk protein inhibitors were collected. Molecular modeling of these 131 molecules was done through Accelrys discovery studio (ADS). Choose appropriate force-field & minimization (Smart, Stephent Descent, and Conjugate Gradient) according to selected molecules. Then collected crystal ligand is purified by protein purification method and used appropriate conformation (BEST, FAST, and CAESAR). Docking methods were analyzed with protein, crystal ligand and similar inhibitors to know the best protein-ligand interaction. Pharmacophore research is done through HIPHOP and HYPOGEN method. Protein with final compound docking method is done after completion of virtual screening method. Pharmacophore research with final molecule was done. Quantitative structure activity relationship (qsar) method is analyzed to know the correlation between the above selective structures. From virtual screening method, best and final compound is analyzed. So, final molecule can be a drug molecule for SYK protein abnormality diseases. However, the scope for fine tuning and optimizing this potent class of syK inhibitors could lead to the generation of new therapeutic agents.

INTRODUCTION: Spleen Tyrosine Kinase (syk) is best known as a non-receptor tyrosine kinase. It mediates signal transduction downstream of a variety of transmembrane receptors including classical immune receptor like B-cell receptor. It is involved B-cell and T-cell function, regulates several biological processes including innate & adaptive immunity and plays also a crucial role in the innate immune response to fungal, bacterial and viral pathogens.

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It is also involved in cell adhesion, mast cell signaling, osteoclast maturation, platelet activation and vascular development, neutrophils and macrophages. It is for instance involved in vascular development where it may regulate blood and lymphatic vascular separation, assembles into signaling complexes with activated receptor at the plasma membrane via interaction between sh2 domains and the receptor tyrosine phosphorylated ITAM domains.

Abnormality of this protein may cause the several diseases like Rheumatoid Arthritis, Naso-pharyngeal Carcinoma, all type of blood cancer (WBC, RBC and platelet), head cancer, neck cancer, breast cancer, gastric cancer and several autoimmune diseases [1-9].

Drug designing is the inventive process of finding new medications based on the knowledge of a biological target. Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy [10-14].

MATERIALS & METHODS:

Linux Operating System: (centOS): Operating system is an interface between hardware and application software. Feature of this operating system are multi-user, multi-tasking, portability, machine-independence, well security & 10 times faster than ordinary operating systems.

Accelrys Discovery Studio (2.5): Discovery studio is a software suite of life sciences molecular design solutions for computational chemists and computational biologists. It makes easier to examine the properties of large and small molecules, study systems, identify leads and optimize candidates.

Furthermore, built on Accelrys pipeline pilot technology, discovery studio enables scientists to rapidly automate routine tasks, integrate third party applications and even deploy models out to research colleagues together, this uniquely positions discovery studio as a truly as a comprehensive collaborate research solutions for both experts and project terms alike.

NCBI: http://www.ncbi.nlm.nih.gov/: The National Center for Biotechnology Information (NCBI) provides a comprehensive website for biologists that includes biology related databases, and tools for viewing and analyzing the data inherent in the databases. NCBI is an agency responsible for creating automated systems for storing and analyzing the rapidly growing profusion of genetic and molecular data.

PDB: http://rcsb.org/pdb/home/: The protein data bank (pdb) was established at Brookhaven national laboratories (BNL) in 1971 as archive for biological macromolecular crystal structure it is the single archive of biological macromolecular structures. The research Collaborator for Structural Bioinformatics (RCSB) has been fully responsible for its management since July 1, 1999.

Molecular Modeling: It is a collective term that refers to theoretical methods and computational techniques to model or mimic the behavior of molecules. The techniques are used in the fields of computational chemistry, computational biology [15, 16].

Force field: A force field is used to calculate the energy and geometry of a molecule. It is collection of atom types (to define the atoms in a molecule), parameters (for bond, lengths, bond angles, etc) and equations (to calculate the energy of a molecule). a set of functions and parameterization used in molecular mechanics calculations, 1st generation Force Field (FF) applicable mainly to biochemistry. 2nd generation FF capable of predicting many properties, rule based FF applicable to a broad range of periodic table. Special purpose of FF narrowly applicable to particular applications or types of models [17, 18]

Minimization: A process by which a molecular structure is brought to minimum energy conformation. It involves iteratively adjusting atomic coordinates until the forces acting on the atoms are zero or close to zero. Minimization generally takes the molecule to the local minimum nearest to the starting conformation [17, 18].

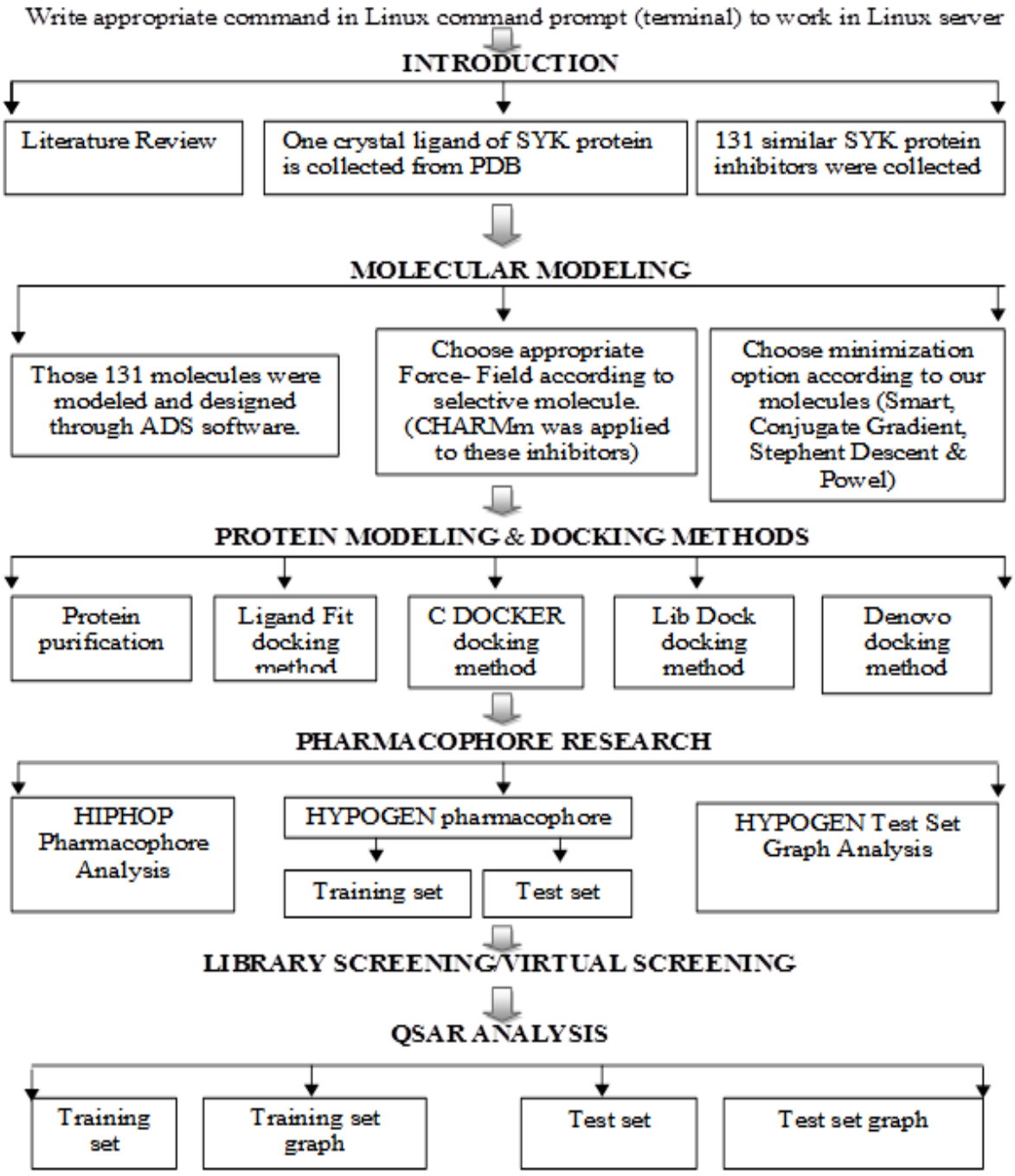
Docking: Docking is an energy optimization process concerned with the search of the lowest free energy binding mode of a ligand within a protein binding site. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. It has 2 components (pose search, scoring).

Pharmacophore: Pharmacophore is an analog based method. This word is coined by Paul Ehrlich in the early 1900s referring to a molecular frame work that carries the essential features (phoros) responsible for a drug's (pharmacon) biological activity. In 1977 Peter Gund redefined as "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity". A pharmacophore can also be generated from the receptor structures.

In dynamic pharmacophore model based on molecular dynamics trajectories takes care of the binding site dynamics. These models can be used for optimizing known ligands or for screening databases to find potential novel leads suitable for further development [19].

Virtual screening: Virtual screening as "automatically evaluating very large libraries of compounds" using computer programs. The aim of virtual screening is to identify molecules of novel chemical structure that bind to the macromolecular target of interest. Virtual screening is very important part of drug design and drug discovery research.[20-23].

Quantitative Structure Activity Relationship (QSAR): Quantitative structure activity relationships (qsar) represent an attempt to correlate structural or property descriptors of compounds with activities. Sufficient number of ligands active against target of intrest should be available to develop the structure activity relationships. The equations that are parameterized for one target do not apply to another.



A TOTAL OVERVIEW OF THIS RESEARCH

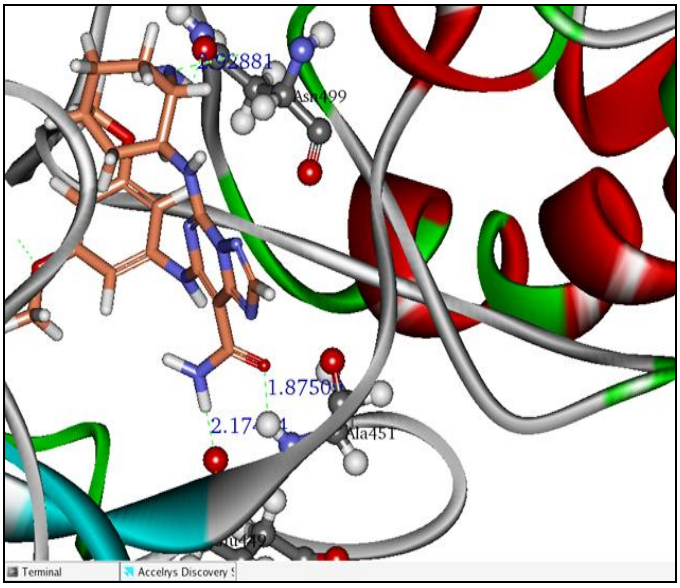


FIG. 1A: MOLECULE SHOWS THE BEST INTERACTIONS WITH IMPORTANT AMINO ACIDS WITH LIBDOCK DOCKING METHOD

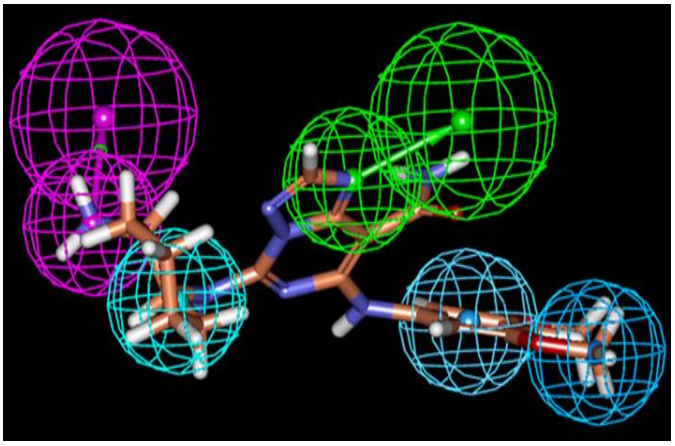


FIG-2: HIPHOP PHARMACOPHORE BEST FIT WITH BEST MOLECULE OBTAINED FROM HIPHOP PHARMACOPHORE RESULT

TABLE 1: HIPHOP EXPORTING HYPOTHESES FROM HIPHOP ALGORITHM

Sl. no.	Features	RANK	DH	PH	MAX.FIT.
1	YZHDA	66.388	11111	OOOOO	5
2	YZZDA	66.218	11111	OOOOO	5
3	YZHDA	65.732	11111	OOOOO	5
4	ZHHDA	64.797	11111	OOOOO	5
5	YZHDA	64.197	10111	O1OOO	5
6	YZHDA	64.197	10111	O1OOO	5
7	ZZHDA	63.946	11111	OOOOO	5
8	YZHDA	63.514	11111	OOOOO	5
9	YZHDA	63.514	11111	OOOOO	5
10	YZHDA	63.388	10111	O1OOO	5

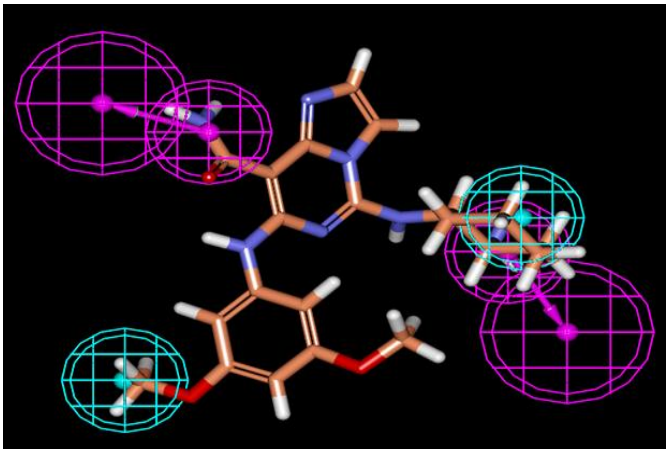


FIG. 3: HYPOGEN PHARMACOPHORE BEST FIT WITH BEST MOLECULE OBTAINED FROM HYPOGEN PHARMACOPHORE RESULT

TABLE 2: HYPOGEN EXPORTING HYPOTHESES FROM HYPOGEN ALGORITHM

Hypo no.	total cost	cost diff.	error cost	RMS	correlation	Feature
1	101.894	43.816	90.9679	0.92382	0.918158	ADHR
2	106.612	39.098	95.8784	1.12368	0.87816	ADHR
3	107.424	38.286	96.6102	1.15049	0.869471	ADHR
4	110.714	34.996	100.059	1.26928	0.838188	ADHR
5	114.234	31.476	103.373	1.37375	0.807539	ADHR
6	116.342	29.368	105.295	1.43087	0.789416	ADHR
7	117.082	28.628	106.422	1.46331	0.777607	ADHR
8	117.331	28.379	106.705	1.47135	0.774749	ADHR
9	117.903	27.807	107.266	1.48714	0.769176	ADHR
10	117.903	27.807	107.266	1.48714	0.769176	ADHR

TABLE 3: IT SHOWS THE BEST HYPOTHESIS OF HYPOGEN TRAINING SET

Comp.no.	FIT	CNF	MAPPING	EST	ACT	ERROR	UNC
1	7.47	1	+[13 31 27 23]	5.7	4	1.4	3
2	7.88	1	+[13 22 18 31]	2.2	6	-2.8	3
3	6.64	1	-[21 * 6 22]	38	8	4.7	3
4	6.19	1	+[7 22 * 26]	110	20	5.4	3
5	6.57	1	+[15 * 6 23]	45	34	1.3	3
6	6.01	1	+[7 21 16 *]	170	60	2.8	3
7	6.37	1	-[15 * 23 6]	72	71	1	3
8	6.54	1	+[13 31 27 *]	48	83	-1.7	3
9	5.92	1	-[15 * 22 6]	200	90	2.3	3
10	6.06	1	+[7 21 16 *]	150	110	1.3	3
11	5.42	1	+[25 * 27 6]	630	160	3.9	3
12	6.09	1	+[15 * 6 22]	140	260	-1.9	3
13	6.18	1	+[* 21 16 33]	110	340	-3.1	3
14	6.25	1	+[13 * 31 5]	95	490	-5.2	3
15	5.18	1	-[* 13 20 27]	1100	680	1.6	3
16	5.38	1	+[25 * 17 6]	700	160	-1.3	3
17	5.53	1	+[13 * 27 47]	490	260	-2	3
18	4.46	1	+[22 * * 5]	5800	340	4.1	3
19	4.45	1	+[22 * * 5]	5900	490	3.1	3
20	4.45	1	+[24 * * 23]	6000	680	-1.3	3
21	4.42	1	+[* * 17 6]	6300	8600	-1.4	3
22	4.41	1	+[27 * 23 *]	6500	13000	-2	3
23	4.47	1	+[* 11 7 *]	5700	25000	-4.4	3
24	4.37	1	-[* 11 6 20]	7100	40000	-5.7	3

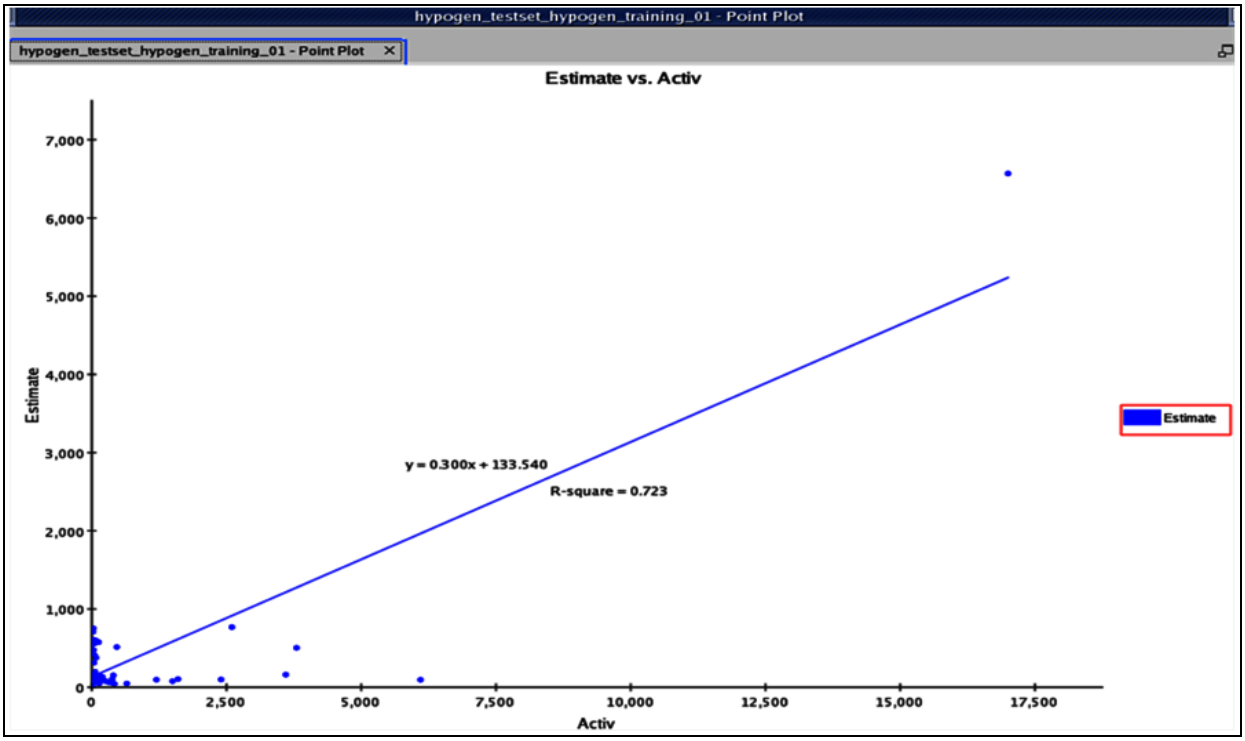


FIG. 4: PHARMACOPHORE HYPOGEN TEST GRAPH

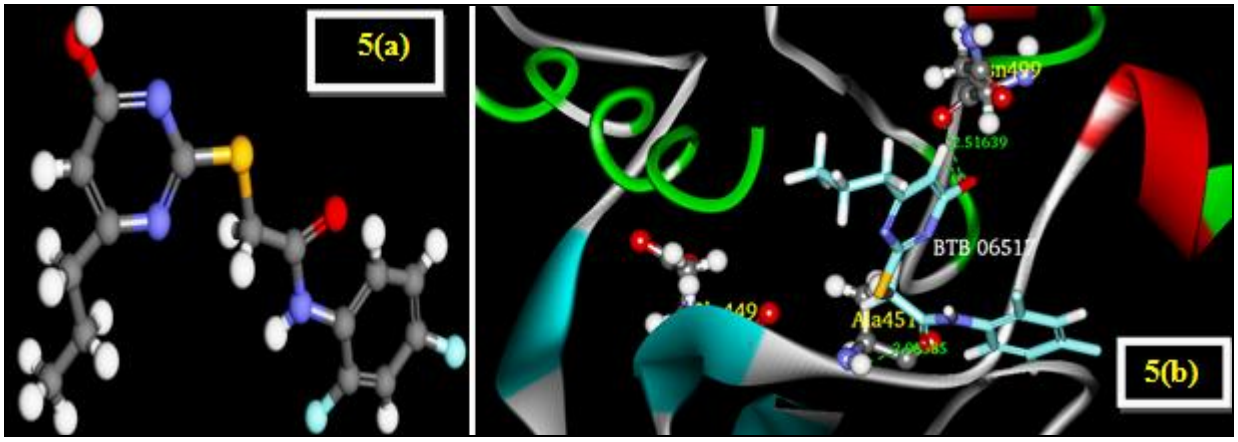


FIG. 5(A) SHOWS THE BEST COMPOUND AFTER SCREENING, FIG. 5(B) SHOWS BEST COMPOUND WITH BEST INTERACTION WITH IMPORTANT AMINO ACIDS WITH LIBDOCK DOCKING METHOD

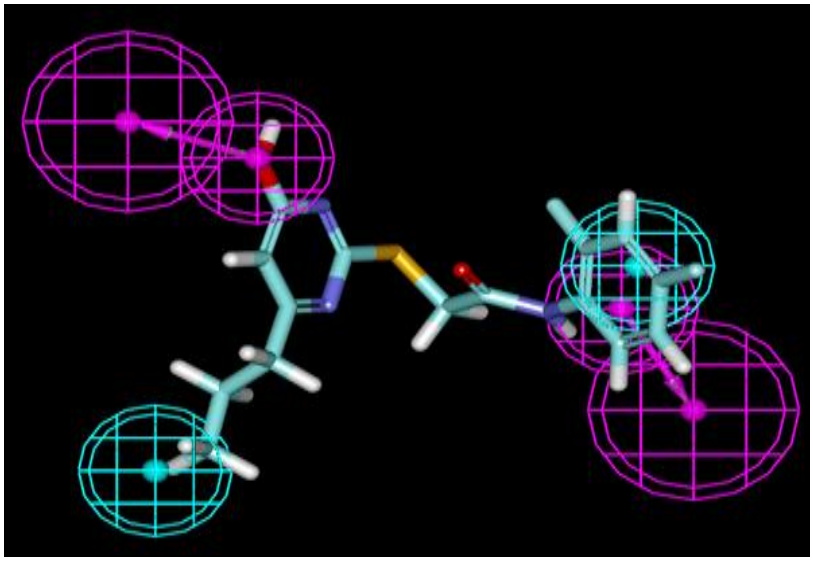


FIG. 6: BEST DRUG MOLECULE WITH BEST FIT RESULT IN PHARMACOPHORE

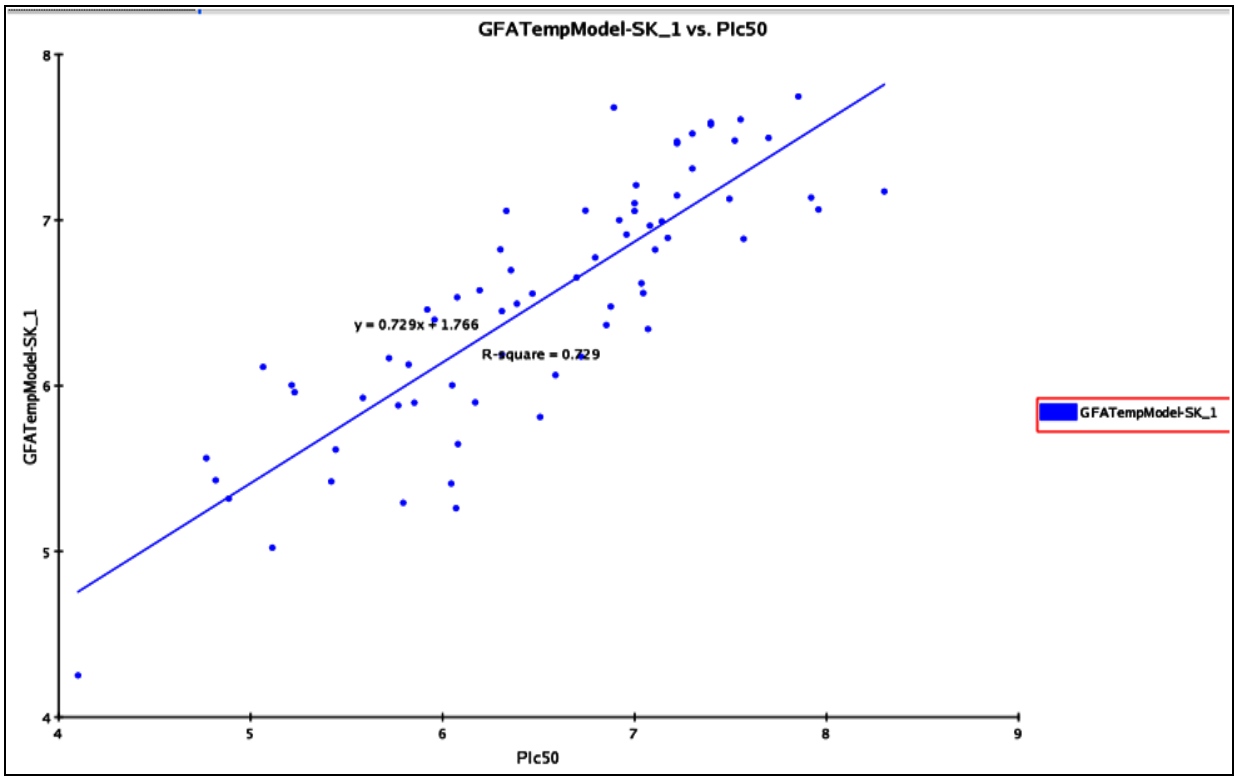


FIG-7: QSAR TRAIN SET GRAPH OBTAINED FROM ADS SOFTWARE

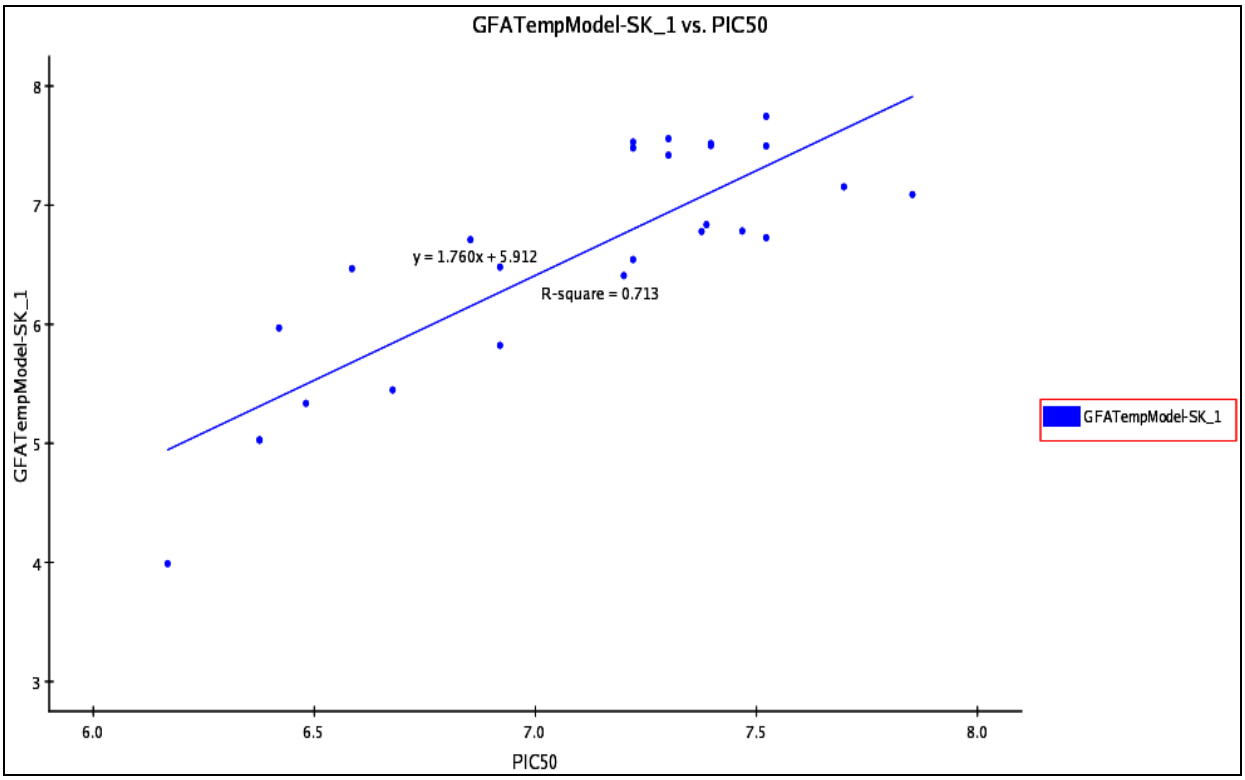


FIG-8: QSAR TEST SET ANALYSIS GRAPH

DISCUSSIONS: Spleen Tyrosine Kinase (SYK) is a protein best known as non-receptor tyrosine kinase. Abnormality of this protein may cause various diseases like Rheumatoid Arthritis, Nasopharyngeal Carcinoma, and all type of blood cancer, head cancer, neck cancer, breast cancer, gastric cancer and several autoimmune diseases. Gene and protein information are analyzed by different online tools, databases (NCBI, KEGG, GeneCards, PDB, Uniprot) and literature review.

One crystal ligand (4DFL - which encodes for SYK protein) is collected from PDB database on the basis of <3.0 resolution, latest and updated, less sequence gap in protein active site, which is mentioned in run ligplot pdf (downloaded from PDB).

From literature review, 131 SYK protein inhibitors were collected. Molecular modeling of these inhibitors is done by Accelrys Discovery Studio. Force fields are 2 types (fitted force fields, rule based).We have to research which is an appropriate Forcefield (CHARm, CHARMm polar H, CVFF, charmm19, charmm22, charmm27, cff, MM3, XPROLIG, MMFF, ESFF, UFF) with respective partial charges for our selective inhibitor molecules. We have to analyze which is the appropriate minimization (Smart, Steepest-descents, and Conjugate-gradients, Powel) and adjusting the steps for our selective inhibitors.

Potential and absolute energy were noted. This above method is called molecular modeling. Then protein is purified (deletion of unnecessary ligands, water molecules, clean protein and so on) by protein purification method. Steepest descent and conjugate gradient minimization is applied one by one and results are noted respectively. We have to analyze which is the most preferable docking method (LIGAND FIT, CDOCKER, LIBDOCK, and DENOVO) for our selective protein.

From 131 molecules, 18 molecules (low, moderate, high energy molecules) were selected and to get an overview which is the best docking method for our selective protein inhibitors. The Results concluded that LIBDOCK docking method is most preferable for SYK protein. In this method high energy molecules are interacting with all important amino acids (GLU 449, ALA 451 and ASN 499) with distance 2.174, 1.8750, 2.92881 respectively shown in **fig. 1**.

In pharmacophore, HIPHOP or common feature pharmacophore method with 6 high energy molecules were selected from 131 SYK inhibitors. At a time 6 molecules were opened in ADS software. 2 attributes (principal, MaxOmitFeat) were added. The features of these attributes are (2-0, 2-0, 1-1, 1-1, 0-2 and 0-2). The minimum interfeature distance of this HIPHOP algorithm is 2.97 with BEST conformation. The features are (hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic (H), hydrophobic aromatic (Y), hydrophobic aliphatic (Z)).which shown in **fig. 2**. HIPHOP exporting hypotheses from HIPHOP algorithm is shown in **Table 1.**

In HYPOGEN method, the total SYK inhibitors are divided in two parts i.e. training set and test set. Two attributes (Active, Uncert) are added in training set and test set, the features of these 2 attributes are (active value, Uncert is 3). In training set 24 low, moderate and high active molecules were selected.Pharmacophore HYPOGEN algorithm with best fit molecule is shown in **fig. 3.** Results obtained from 10 hypotheses of HYPOGEN algorithm. Total cost, cost difference, error cost, RMS, correlation, feature (ADHR) are noted, shown in **table 2.**

Out of these 10 hypothesis was considered as the best due to high cost difference from that null hypothesis. From our best result where total cost is 101.894, cost difference is 43.816, error cost is 90.9679, RMS is 0.923821, and correlation is 0.918158. Cost difference is calculated by this formula (null cost-total cost), shown in **table 3.** Another 107 molecules are taken as test set. From this 107 molecules pharmacophore HYPOGEN test graph was obtained. Further validation of the hypothesis was done using the test set molecules for ligand pharmacophore mapping.

A graph was plotted between activity and estimated activity, where R^2 value is 0.723 (according to our rule R^2value must be equal or greater than 0.7), shown in **fig. 4**. In virtual screening/library screening method all molecules were selected. In that database ADS will create 2000 similar molecules as per our selected SYK inhibitors. The features of virtual screening are input ligand is all ligand, input type is database, minimum features is 4, maximum features is 5, maximum subset of pharmacophore is 100, minimum inter feature distance 2.0, fitting method is rigid and with BEST conformation.

From that database, it will find 4-5 best compounds. From these compounds, we have to analyze which is best molecule for abnormality of SYK protein. Results concluded that BTB06517 is the best compound, shown in **fig. 5(a)** where absolute energy is 55.2114; estimate value is

25348.5; best fit value is 3.81925; relative energy is 4.5031. In LIBDOCK docking it is interacting with important amino acids ASP 499, ALA 451 with distance 2.51639, 2.98385 respectively, shown in **fig. 5(b).**

Pharmacophore research is analyzed with this drug molecule which shown in **fig. 6.** The 3D QSAR research conducted for training set gave good R^2 values of 0.729 with MLR graph with a fit that representing the good correlation of the compounds with the activities. QSAR 2D and 3D were analyzed with our selected total molecules. In QSAR we have divided into training and test set with 2:1(85:46) ratio.

The molecular properties are AlogP, molecular_weight, Num_aromatic rings, Num_H_Acceptors, Num_H_donor, Num_rings, Num_rotatable bonds, molecular functional polar surface area, Dipole_mag, Dipole_X, Dipole_Y, Dipole_Z, Jurs_DPSA_1, Jurs_DPSA_2, Jurs_DPSA_3, Jurs_FNSA_1, Jurs_FNSA_2, Jurs_FNSA_3, Jurs_FPSA_1, Jurs_FPSA_2, Jurs_FPSA_3, Jurs_PNSA_1, Jurs_PNSA_2, Jurs_PNSA_3, Jurs_PPSA_1, Jurs_PPSA_2, Jurs_PPSA_3, Jurs_RASA, Jurs_RNCG, Jurs_RPCS, Jurs_RPSA, Jurs_SASA. After calculations of molecular properties one PIC50 attribute is added. PIC50 value is calculated by this formula "9-log (active value of molecule)".

In training set molecules were taken as the 2D molecular properties were calculated. The multilinear regression algorithm was applied and a graph was plotted between activity and the QSAR_MLR model obtained, where R^2 value is 0.729, shown in **fig. 7.** Result of all 46 molecules taken as test set. With the help of train set result and with same procedure followed for test set. QSAR test set graph is shown in **fig. 8.**

CONCLUSION: *In silico* drug design studies considered for SYK protein. The algorithms such as MOLECULAR MODELING, PROTEIN PURIFICATION, DOCKING, PHARMACO-PHORE, VIRTUAL SCREENING and QSAR were used. These algorithms showed good results and further investigation for the drug collaboration can be done. Results concluded that BTB06517 compound having good interactions with docking method. It had a good potential, best fit with other molecules and best fit with our pharmacophore result. So this compound may be a drug molecule for SYK (Spleen Tyrosine Kinase) abnormality diseases. Lead optimization and lead to the generation of a highly potent series of SYK inhibitors with good drug like properties. However, the scope for fine tuning and optimizing this potent class of SYK inhibitors could lead to the generation of new therapeutic agents.

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