AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

QSAR STUDY OF SYK (SPLEEN TYROSINE KINASE) INHIBITORS.

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ABSTRACT

Spleen Tyrosine Kinase (SYK) is known to play vital role in many signal transduction pathways and hence is considered as a potent target for various disorders like inflammatory, cancer and many auto immune disorders. QSAR study of Napthyridines as SYK Kinase inhibitors was performed using accelrrys discovery studio client (DSV - Version 3.0) as the modelling tool. A total of 53 selected molecules were considered for the development of QSAR model. The study was performed using the most stable confirmer fitting best to SYK Kinase enzyme binding site. The study resulted in development of cross validated QSAR models using different set of descriptors. Partial least square model of the data generated exhibited a very good linear relation between the training set of compounds with that of the reported activity as well as the test set of compounds with the predicted activity. The 4 statistical analysis performed revealed following observations; Training data set r^2= 0.848, q^2 (Cross validated r^2) = 0.581 validated by internal validation with correlation of coefficient (r2) of 0.941 and cross validated r2 (q2) of 0.617 and external set of compounds with a predictive correlation of coefficient of 0.918. A total of 11 descriptors pruned on the study explained the structural correlation of Napthyridines with SYK Kinase enzyme. The mode developed can be used to predict bio-efficacy of unknown molecules 7-methoxy-6-[3-morpholinopropoxy]-quinazoline as SYK Kinase inhibitors. The study calls for the development of the molecules predicted as bio efficacious in this model and a quantitative inhibitory analysis of SYK Kinase.

Key words: Napthyridines, QSAR, SYK.

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Received 15 July 2011, Accepted 29 July 2011

Please cite this article in press as: Kakadiya P *et al.*, Studies on QSAR Study of SYK (Spleen Tyrosine Kinase) Inhibitors. American Journal of PharmTech Research 2011.

INTRODUCTION

A protein kinase is an enzyme which catalyses phosphorylation reaction i.e., it can transfer phosphate group from ATP to amino acid residue of a protein. Phosphorylation of the kinase accelerate or decelerate the enzymatic activity[1].

Syk (spleen tyrosine kinase) is a non-receptor protein tyrosine kinase that has, at the N-terminus, a tandem pair of Src homology 2 (SH2) domains separated by a long linker (linker B) from the C-terminal catalytic domain. Syk is one of two members of the Syk-family of kinases, the other being ZAP-70. An alternatively spliced variant of Syk, SykB, lacks a stretch of 23 amino acids from linker B. Syk prefers to phosphorylate substrates on tyrosines surrounded by acidic amino acids[1]. Syk is expressed in most hematopoietic cells including B cells, thymocytes, erythrocytes, monocytes, macrophages, leukocytes, natural killer cells, eosinophils, mast cells and basophils, but is largely absent from mature T cells. It is also expressed in epithelial cells and in some neuron-like cells, hepatocytes, and endothelial cells. Syk B is found most abundantly in bone marrow-derived B cells and epithelial cells[2].

In hematopoietic cells, Syk is required for transducing signals from a wide variety of cell surface receptors involved in the recognition of antigens or antigen-antibody complexes. In Syk-deficient mice, B cell development is blocked due to a lack of signal from pre-B and B cell antigen receptors. Syk-deficient mast cells are unable to de-granulate when triggered through the high-affinity IgE receptor, FcεRI. Phagocytosis through Fcγ receptors is blocked in Syk-deficient macrophages as is the FcγR-stimulated production of reactive oxygen species. FcR-dependent immune complex internalization is blocked in dendrite cells from Syk-deficient mice as is the activation and aggregation of platelets via the collagen receptor. Syk associates with the B cell and T cell antigen receptors, FcεRI, FcγRI, FcγRIIa, FcγRIIIa, NK cell activating receptors and collagen receptor through the binding of its tandem SH2 domains to a conserved pair of tyrosines present within an immuno-receptor tyrosine-based activation motif (ITAM) found on the cytoplasmic tails of receptor components. ITAMs bear the consensus sequence E/DXXYXX(L/I)X6-8YXX(L/I) and bind Syk when both tyrosines are phosphorylated, typically by a Src-family kinase in conjunction with Syk, itself. In addition, Syk associates with β-integrins and the receptors for IL-2, G-CSF, GM-CSF, IL-3, IL-5, IL-15, and tumor necrosis factor (TNF). In Syk-deficient mice, integrin-dependent signaling in monocytes and neutrophils is defective. Syk-deficient mice exhibit a perinatal lethality resulting from a failure of the circulatory and lymphatic systems to separate during development[3-4].

Syk is localized in resting cells in both the nucleus and cytoplasm and is recruited from both compartments to the site of the aggregated, ITAM-containing receptor. The binding of Syk to phosphorylated ITAMs on cross-linked receptors leads to its activation and its phosphorylation on multiple tyrosines. The phosphorylations of tyrosines in the activation loop of the catalytic domain are important for receptor-mediated signaling. The phosphorylation of linker B region tyrosines provides docking sites for downstream effectors that bear SH2 or related domains. The binding of c-Cbl, an E3 ubiquitin ligase, to phosphotyrosine-317 (mouse) inhibits Syk-dependent signaling. The C-terminal SH2 domain of the p85 subunit of phosphoinositide 3-kinase can also bind here. Tyrosines-342 and -346 constitute a multi-functional binding site that interacts with SH2 domains from the guanine nucleotide exchange factor, Vav1, phospholipase C-γ (PLCγ) and the Src-family kinase, c-Fgr. Vav1 can bind phosphotyrosine-342 alone while PLCγ binds only when both tyrosines are phosphorylated. Syk also binds CrkL and Gab2[5-7].

Syk is expressed in normal breast epithelial cells and in relatively benign breast cancer cells, but is missing from highly metastatic cells due to gene methylation. Re-expression of Syk in malignant breast cancer cells reduces their tumorigenicity, decreases cell motility and enhances cell-cell adhesion. Syk functions, in part, through its ability to associate with and inhibit signaling from the EGF receptor[8].

Derivatives of [1,6] napthyridines have been studied for their structure activity relationship as Syk inhibitory activity. Structure activity study of [1,6] napthyridines reported a 7-aryl and preferably Para-substituted aryl group as well as 5-alkyldiamines have synergistic effects on activity[9]. Quantitative structure-activity relationship (QSAR) study is basically concerned with the correlation of structure and property/activity. Several molecular descriptors are used to quantify the structural features of lead molecule. The purpose of using QSAR-Descriptors is to calculate the properties of molecules that serve as numerical descriptions or characterizations of molecules in other calculations such as diversity analysis or combinatorial library design. In view of the above facts and to quantify the structural features required for the [1, 6] napthyridines derivatives to inhibit Syk kinase, we report QSAR study of [1, 6] napthyridines with the objective to develop a significant model to predict Syk kinase inhibitors.

MATERIALS AND METHODS

All computational work was performed on Pentium IV workstation-using Discovery Studio Client (DSV v3.0), developed by Acclerys software Inc., Japan. A total of 59 compounds were selected for the present study. All the compounds was drawn using Molecule Window and

Sketching tool and then subjected to conformational analysis and energy minimization using prepare ligand protocol. Since each molecules possess more than one conformation From this list the conformer with lowest absolute energy was selected, the lowest energy conformer in the conformation database of the particular molecule is considered the most stable conformation and the best conformation for the QSAR study for that molecule, hence a database is created from the lowest energy conformer of each molecule. Lowest energy conformer was transferred to molecule window and molecular descriptors were calculated. DSV calculates 560 sub-descriptors from three major classes of descriptors; – 1D descriptor 2D descriptors, 3D descriptors[10].

59 Napthyridines derivatives were divided into two sets. 53 compounds were taken in for the training set (Table **1**) and 6 compounds were taken in for the test set (Table **2**). IC50 values for SYK kinase inhibition were transformed into –log (IC50*10-6) *i.e.* pIC50. The QSAR model was developed using pIC50 as activity field and partial least square (PLS) method for performing regression analysis. PLS regression method was used to analyze the internal interaction between the data matrices including the independent variable matrix of molecular descriptors of DSV and the dependent variable matrix of pIC50. The PLS algorithm transforms the original variables into PLS components from dataset, such that each PLS component is correlated with the dependent data to a maximal possible extent. Statistical parameters like r^2 (Coefficient of correlation) and q^2 (Cross-Validated coefficient of correlation) were obtained after fitting the data by PLS. The model was cross validated to get prediction values, residual values. Cross validated cross validated r2 (q2) were also obtained. Using the prediction fit performed in training set model; predicted pIC50 values of test set were evaluated. Out of 560 descriptors, 11 sub-descriptors, pruned from 4 major descriptor sets were selected and are listed in Table 3. The model developed was optimized using LOO (Leave One Out method). Use of different set of descriptors and sub-descriptors are particularly requires the model to be validated by external predictive power i.e. external prediction is address the latent variables in case of PLS analysis. Hence, a set of 6 molecules covering different napthyridines derivatives was employed as test set to evaluate the predictivity of training set. After validate the model predict the activity of the unknown molecule as a SYK inhibitor. Here basic moiety selected for the derivatization was 7-methoxy-6-(3-morpholinopropoxy)-quinazoline-4-one. First create the database of the new molecule and then the new derivatives thus generated were incorporated into the test data set and

their activity was predicted on the basis of the PLS model generated for the training set. pIC50 value is a measure of the potency of the compound.

Different sets of sub-descriptors employed in this study, met the orthogonality of the model, which ensures that each descriptor is encoding different properties from others. Traditional descriptors such as, log P *etc*., are more relevant to drug transport or pharmacokinetics than the receptor affinity. Further, traditional descriptors consider the whole molecules property rather than the distinguishing details of sub-structural differences.

RESULTS AND DISCUSSION

Training set of 53 derivatives of Napthyridines, which represents Napthyridines with structural modification on aliphatic and aromatic amine, and substituted phenyl attached to core nucleus were employed. A test set of 6 molecules used for evaluation, encompassed a wide range of structures to validate the model. Correlation Plot of pIC50 between experimental values and the predicted values in training set is shown in Figure 1. Also, Correlation Plot of pIC50 between experimental values and the predicted values in test set by considering the model developed by training set (model fit) is shown in Figure 2.

Following statistical measures were used to correlate biological activity and molecular descriptors:

N = number of samples, r^2 = coefficient of correlation, q^2 = cross validated coefficient of correlation, r^2 pred. = coefficient of correlation of test set.

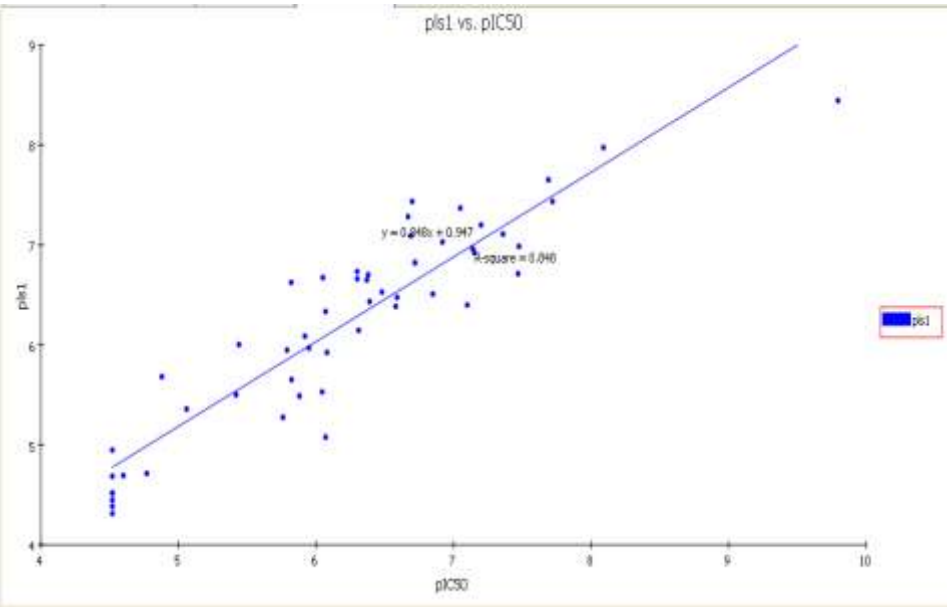


Figure 1**:** PLS Molecular Point Plot for training set

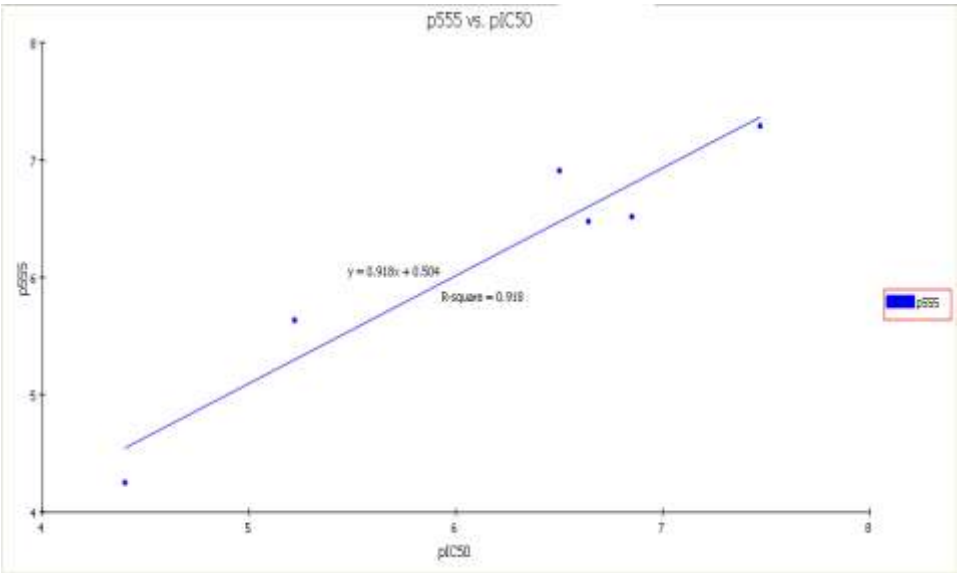
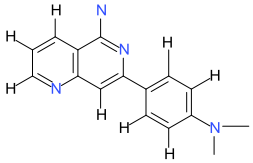
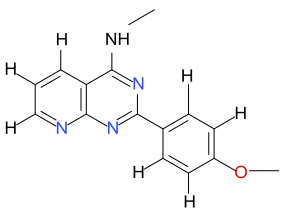
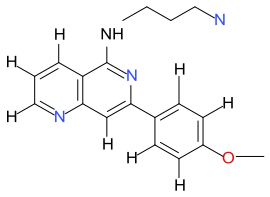
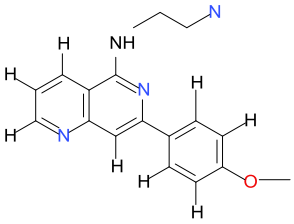
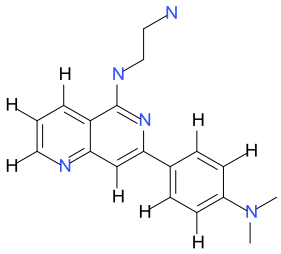
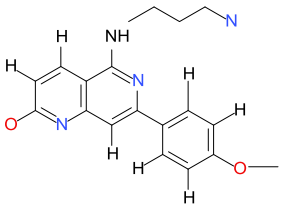
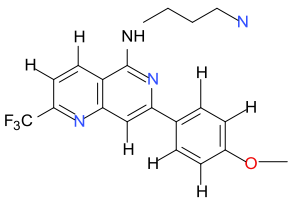
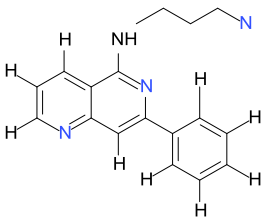


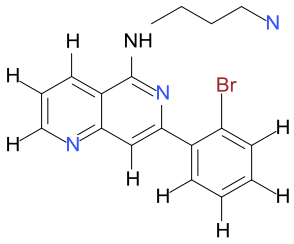
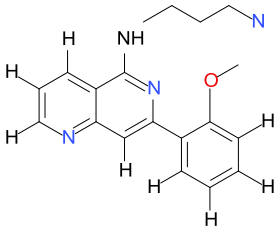
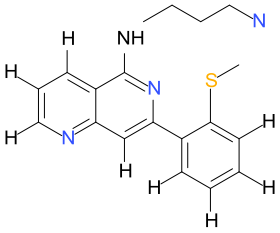
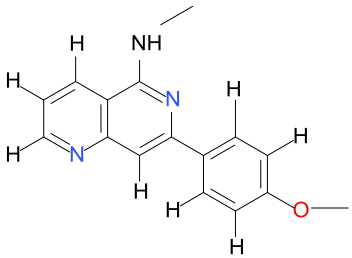
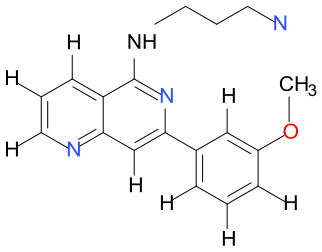
Figure 2**:** PLS Molecular Point Plot for Test set

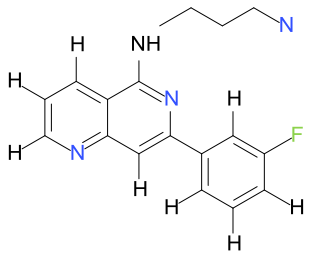
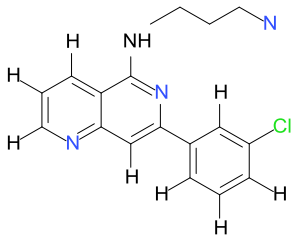
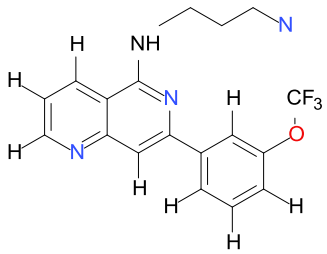
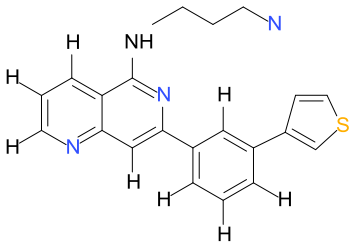
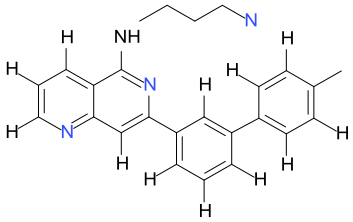
Model developed has a correlation of coefficient (r^2) of 0.848 and cross validated r^2 (q^2) of 0.581. The model developed predicts 68.51% of variance and is validated by internal validation with correlation of coefficient (r^2) of 0.941 and cross validated r^2 (q^2) of 0.617 and external set of compounds with a predictive correlation of coefficient of test set is 0.918. Results comparing observed and predicted pIC50 along with residual values are shown in Table 1. The predictivity of model evaluated by test set of compounds is mentioned in Table 2.

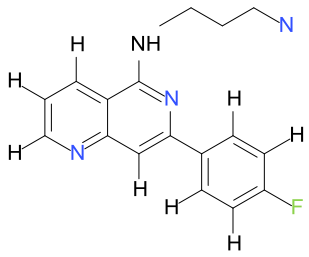
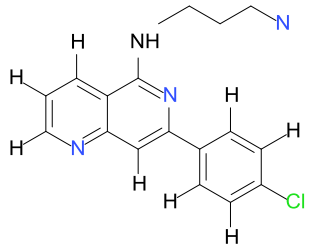
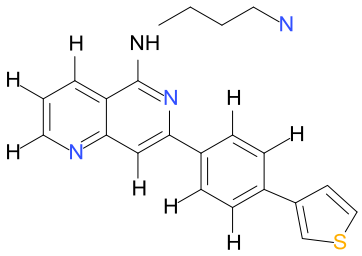
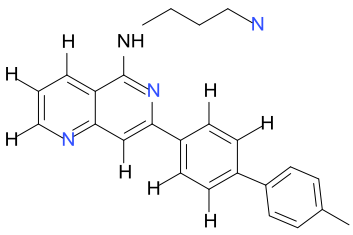
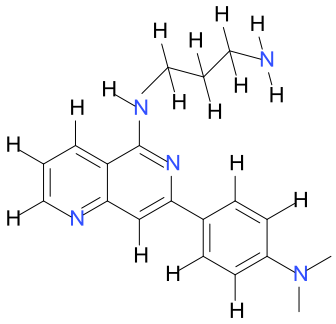
Table 1. Structures, Experimental and Predicted Activity of [1, 6] napthyridines Used in Training Set for SYK Inhibition

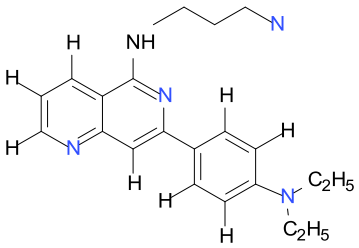
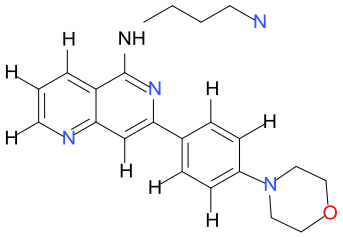
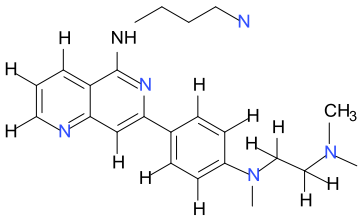
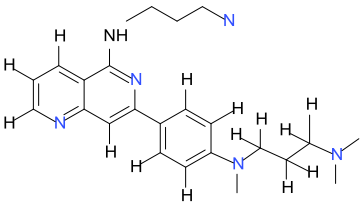
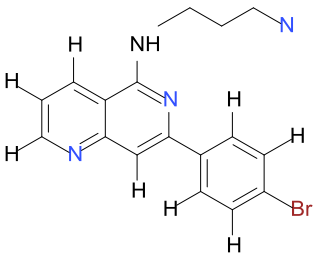
Sr No.	Name	Structure	Experimental pic50	Predicted pic50	Residuals
1.	pra_syk 35		6.72	6.82367	-0.103669
2.	pra_syk 23		4.52	4.52116	-0.00116475

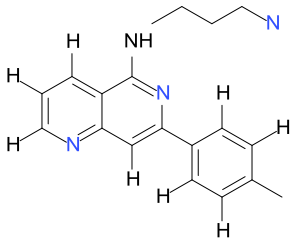
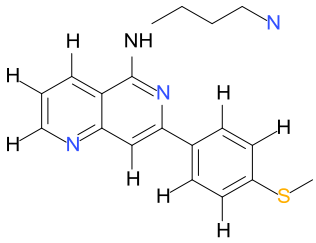
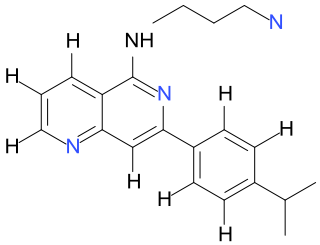
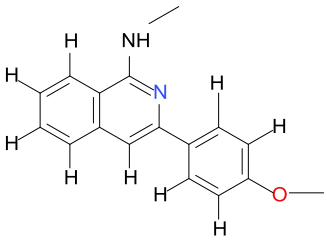
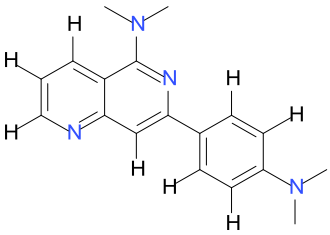
3.	pra_syk 33		6.85	6.51	0.340004
4.	pra_syk 1		5.82	6.62609	-0.806092
5.	pra_syk 2		6.72	6.82367	-0.103669
6.	pra_syk 3		4.52	4.68792	-0.167919
7.	pra_syk 4		4.52	4.51502	0.00498373
8.	pra_syk 8		6.39	6.43447	-0.0444687

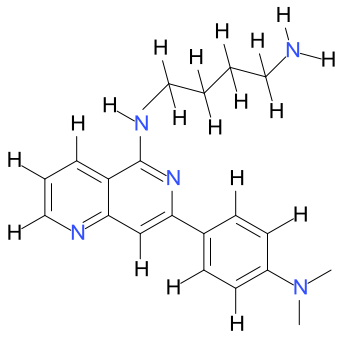
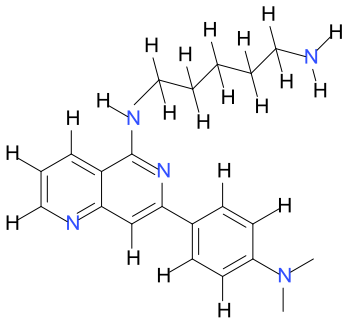
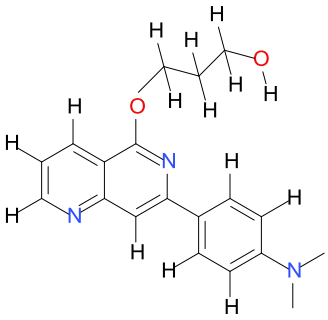
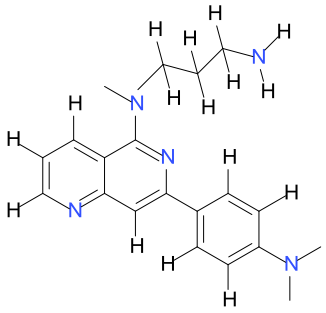
9.	pra_syk 9		4.6	4.69455	-0.094554
10.	pra_syk 10		4.52	4.44866	0.0713352
11.	pra_syk 11		4.52	4.94986	-0.429862
12.	pra_syk 12		6.31	6.14699	0.163006
13.	pra_syk 13		6.3	6.66156	-0.361563

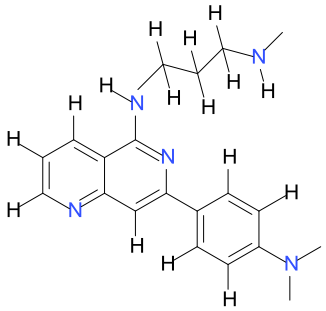
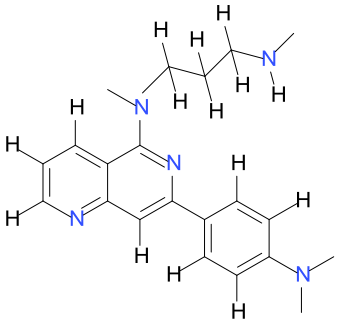
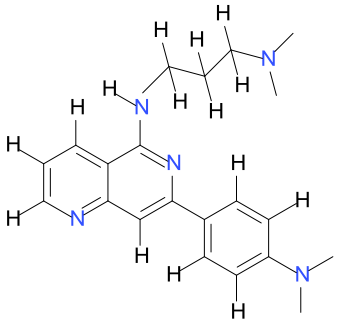
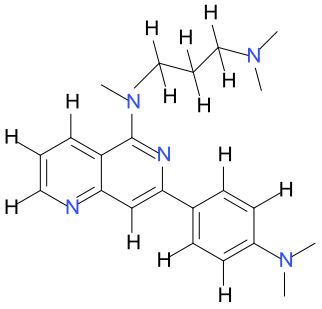
14.	pra_syk 14		6.07	6.33542	-0.265421
15.	pra_syk 15		6.59	6.47618	0.113818
16.	pra_syk 16		6.08	5.92539	0.154609
17.	pra_syk 17		5.823	5.65401	0.168987
18.	pra_syk 18		5.42	5.50258	-0.0825821

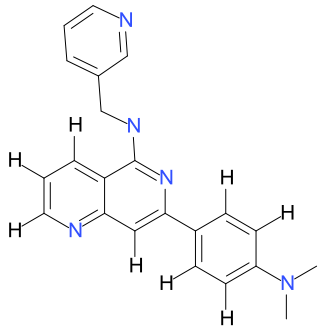
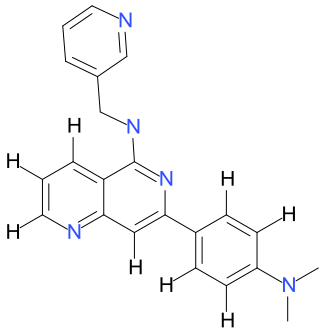
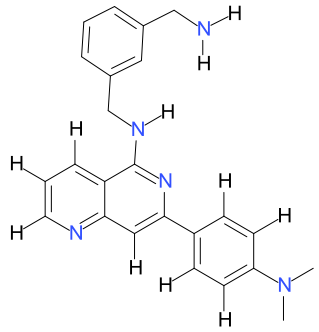
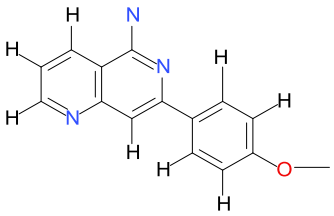
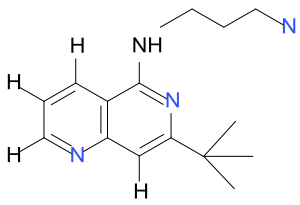
19.	pra_syk 19		5.95	5.96941	-0.019413
20.	pra_syk 20		5.92	6.08776	-0.167759
21.	pra_syk 21		5.79	5.9494	-0.159397
22.	pra_syk 22		6.045	5.53088	0.514124
23.	pra_syk 24		7.47	6.71266	0.757343

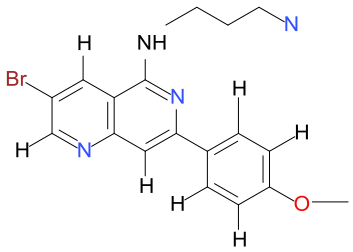
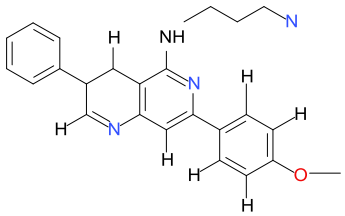
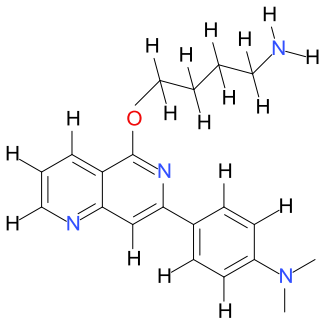
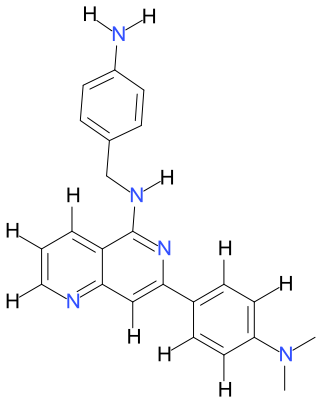
24.	pra_syk 25		7.69	7.65235	0.0376456
25.	pra_syk 26		8.09	7.97559	0.114414
26.	pra_syk 27		7.15	6.92655	0.223449
27.	pra_syk 28		6.37	6.65032	-0.280319
28.	pra_syk 29		6.58	6.38629	0.19371

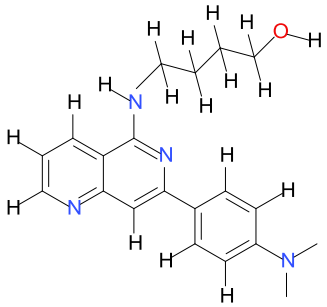
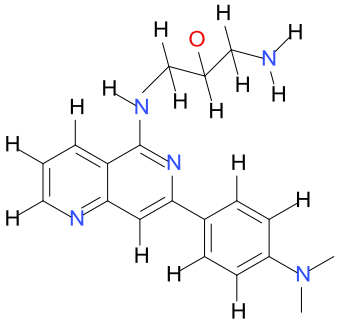
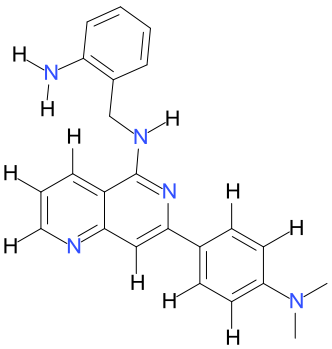
29.	pra_syk 30		7.2	7.20024	-0.000235505
30.	pra_syk 31		7.476	6.98585	0.490148
31.	pra_syk 32		7.05	7.36928	-0.319276
32.	pra_syk 34		4.52	4.31533	0.20467
33.	pra_syk 37		6.38	6.70304	-0.323045

34.	pra_syk 38		7.72	7.43566	0.28434
35.	pra_syk 39		6.67	7.28327	-0.613272
36.	pra_syk 40		6.69	7.09334	-0.403345
37.	pra_syk 43		7.14	6.9621	0.177897

38.	pra_syk 44		7.1	6.40009	0.699912
39.	pra_syk 46		6.05	6.67408	-0.624079
40.	pra_syk 47		5.76	5.27699	0.483006
41.	pra_syk 48		5.06	5.35909	-0.299088

42.	pra_syk 52		5.88	5.48947	0.390534
43.	pra_syk 53		6.3	6.73522	-0.43522
44.	pra_syk 54		6.48	6.53004	-0.0500386
45.	pra_syk 56		4.77	4.71621	0.0537919
46.	pra_syk 59		4.52	4.38481	0.135188

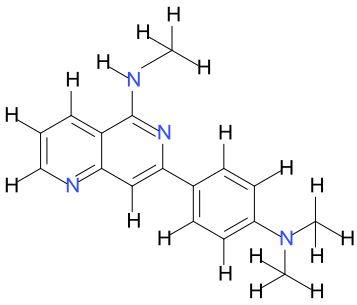
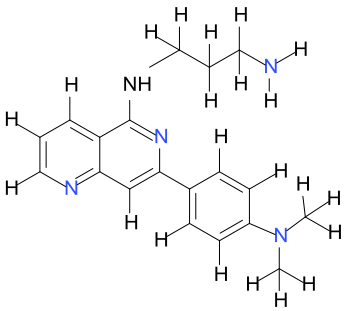
47.	pra_syk 5		6.92	7.02994	-0.109941
48.	pra_syk 6		5.44	6.00424	-0.564243
49.	pra_syk 41		9.795	8.44468	1.35032
50.	pra_syk 57		4.88	5.68331	-0.803311

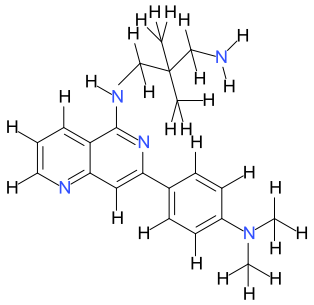
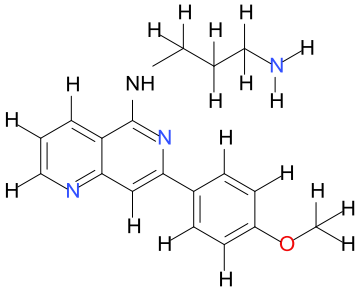
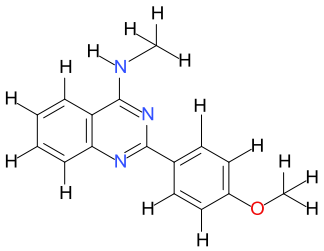
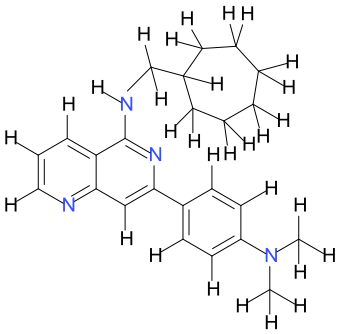
51.	pra_syk 49		6.7	7.43566	-0.73566
52.	pra_syk 51		7.36	7.1101	0.2499
53.	pra_syk 58		6.07	5.07853	0.99147

11 sub-descriptors pruned from 4 major groups of descriptors were adequate to explain different properties of napthyridines moiety. The Major group of descriptors involved sub groups like ALogP, Molecular properties, Molecular property counts and Topological descriptor in Table 3. Molecular properties are descriptor counts the molecular mass, solubility, weight, Pka etc. AlogP predicts log p of molecules parameterizing the contributions of various atoms to the overall molecular partition coefficient using constrained least squares fitting to a training set of compounds with experimentally measured partition coefficients. In order to get reasonable correlations, the most common elements contained in drugs(hydrogen, carbon, oxygen, sulphur, nitrogen and halogens) are divided into several different atom types depending on the environment of the atom within the molecule. Alogp provides a rough estimate for a wide variety of molecules. Molecular property count calculates of the number atoms, bonds, rings, chains,

hydrogen acceptor and donors, etc. in the molecules that are necessary for a molecule to perform biological activities under consideration. Topological descriptors are a special class of descriptors that do not rely on a three-dimensional model. In Discovery Studio there are several topological descriptors that fall into the following classes: Balaban Indices, Wiener Index, Zagreb Index, Connectivity Indices, Graph-Theoretical Info Content descriptors, Kappa Shape Indices, Sub graph Counts. In which Balaban indices is a highly discriminating descriptor, whose values do not substantially increase with molecule size or the number of rings present and Graph-Theoretical Info Content descriptors is info Content descriptors help to differentiate molecules according to their size, degree of branching, flexibility, and overall shape using graph-theory concepts.

Table 2. Structures, Experimental and Predicted Activity of [1,6] napthyridines Used in Test Set for SYK Kinase Inhibition

Sr no.	Name	Structure	Experimental pic50	Predicted pic50	Residuals
1.	pra_syk 36		6.64	6.47741	0.16259
2.	pra_syk 42		7.47	7.29081	0.179191

3.	pra_syk 50		6.5	6.90872	-0.40872
4.	pra_syk 7		6.85	6.51699	0.333014
5.	pra_syk 45		4.4	4.25072	0.14928
6.	pra_syk 55		5.22	5.63535	-0.415355

In tyrosine kinase family, Syk are cytosolic non-receptor tyrosine kinase. Syk is present in platelets, mast cell, B lymphocytes, Basophills, neutrophills, dendritic cells, macrophages and monocytes. Syk kinase has functional role in signal transduction mediated by immuno-receptor tyrosine based activation motif expressed in hematopoietic cells. Syk family tyrosine kinase inhibitors are candidate therapeutic agents for the treatment of various allergic and autoimmune disorders.

Table 3: Molecular Descriptors Used in Present Study:

Sr .no.	Descriptors	Description
2D Descriptors : Use the atoms and connection information of the molecule for the calculation		
ALogP Descriptors		
1.	ALogP	Log of the octanol-water partition coefficient using Ghose and Crippen's method.
2.	ALogP_Count	An array of 120 numbers that correspond to the 120 Ghose and Crippen atom types. The content of each array element is the number of times that particular atom type was seen in the molecule.
Molecular property count descriptors		
3.	Num_Explicit Bonds	Explicit Bonds
4.	Num_H_Acceptors	Hydrogen Bond Acceptors are defined as hetero atoms (Oxygen, Nitrogen, Sulphur, or Phosphorus) with one or more lone pairs, excluding atoms with positive formal charges, amide and pyrrole-type Nitrogens, and aromatic Oxygen and Sulphur atoms in heterocyclic rings.
5.	Num_H_Donors	Hydrogen Bond Donors are defined as hetero atoms (Oxygen, Nitrogen, Sulphur, or Phosphorus) with one or more attached Hydrogen atoms.
6.	Num_Atom Classes	Different atom classes from symmetry perception (excluding hydrogens). For example, benzene would have a value "1" and toluene would have a value "5".
Molecular properties		
7.	Molecular Solubility	Molecular solubility expressed as logS, where S is the solubility in mol/L. The method used to estimate the solubility is the published multiple linear regression model
Topological Descriptors		
8.	JX	Balaban Indices
9.	CIC	Graph-Theoretical InfoContent descriptors
10.	IAC_Total	Graph-Theoretical InfoContent descriptors
11.	E_DIST_equ	Graph-Theoretical InfoContent descriptors

The ATP binding site of Syk based on published crystal structure of activated Lck kinase 1 reviles useful information by the virtue of which different binding interaction of quinazoline derivatives in comparison to establish Syk inhibitor like staurosporine can be understood.

Syk provides three binding interaction namely A, B and C, where in site A and site Bare formed due to by interaction of aromatics rings with methylene or methyl groups C-H π interaction with methyl group of valine352 with indol skeleton of staurosporine can be assimilated by the interaction of aromatic ring of thiol group and the predicted compound, that is amino phenothiol derivative of 7-methoxy-6-(3-morpholinopropoxy)-quinazoline. shown in Figure 3.

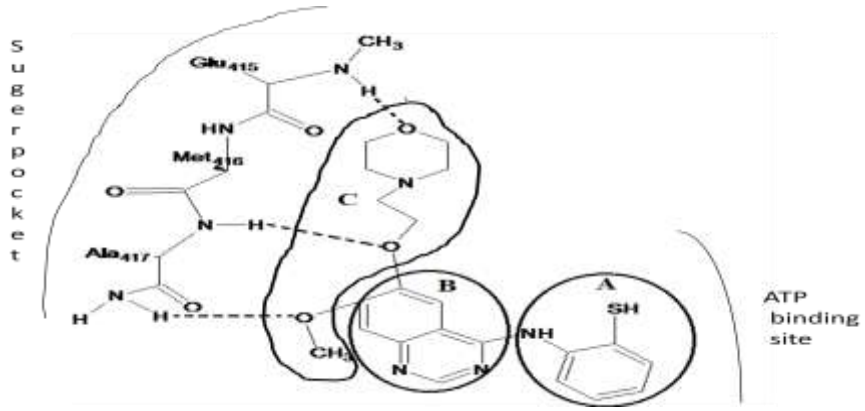


Figure 3: Hypothetical interaction

Similarly, sugar pocket of the enzyme highly interaction of heteroatom of the enzyme and drug are addressed by N and O, etc. atoms of methoxy group and morpholino propoxy group of proposed compound.

This possible interaction of the drug with the ATP binding site of the enzyme provides possible docking interaction of the drug. Enhance observed pIC_{50} value (6.58) is quite justifiable.

CONCLUSION

In conclusion, the model developed to predict the structural features of napthyridines to inhibit SYK Kinase reveals useful information about the structural features required for the molecules. In the models developed AlogP, molecular properties, molecular property Count, topological descriptors were the major contributing descriptors. Descriptor values obtained helps us to understand the structural features required by ATP binding site of SYK Kinase. Since a wide range of structures were incorporated in the training set, molecular Property Count, Topological descriptors also influenced the predictivity of model and that derived model is to predict the activity of unknown molecule as a SYK inhibitor. The results obtained from QSAR study consider not only wide range of structures, but also various physicochemical interactions involved in enzyme inhibitor complex. Hence the model proposed in this work is useful in describing QSAR of nepthyridine derivatives as SYK Kinase inhibitors and can be employed to design new molecule with specific inhibitory activity as a SYK inhibitor.

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