TARGETING RSK2 FOR TREATMENT OF OSTEOARTHRITIS - AN IN SILICO STUDY.

A thesis submitted in partial fulfillment of the

Requirements for the degree of

Bachelor of Technology

In

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By

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Certificate of Approval

This is to certify that the thesis entitled "TARGETING RSK2 FOR TREATMENT OF OSTEOARTHRITIS - AN IN SILICO STUDY" submitted by Mr. Kanhu Charan Biswal in partial fulfilment of the requirements for the degree of Bachelor of Technology in BIOTECHNOLOGY embodies the bonafide work done by him in the final semester of his degree under the supervision of the undersigned. The thesis or any part of it has not been submitted earlier to any other University / Institute for the award of any Degree or Diploma.

Prof. (Dr.) MUKESH KUMAR GUPTA

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Date:

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"Every effort is motivated by an ambition and all ambitions have an inspiration behind in the height of reaching a mile-stone in life."

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Kanhu Charan Biswal (111BT0016)

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ABBREVIATIONS

Name	Full form
RSK2	Ribosomal protein kinase
2D	Two Dimensional
3D	Three Dimensional
QSAR	Quantitative structure activity relationship
IC50	Inhibitor concentration about 50%
ERK	Extracellular signal-regulated kinases
OA	Osteoarthritis
CADD	Computer Aided Drug Designing

Abstract

Osteoarthritis (OA) is the prominent cause of joint pain in elderly patients, exhibited by continuous degradation of articular cartilage; consequently resulting in the loss of cartilage specific type II collagen (CII) and over expression of Rsk2. Rsk2 is considered to be the regulator of bone formation in vivo. Since, Rsk2 plays a pivotal role in the loss of functional and structural integrity of cartilage, hence, inhibiting Rsk2 would seem to be a prudent therapeutic tool. Therefore, this study mainly highlights the complex interaction between the ligand and the protein by examining the ligand links. Moreover, docking and 2D-QSAR methods will act as a useful and informative resource in getting the pharmacophore band structure. Comparative study of docking resulted in considering Phosphoaminophosphonic acid to be a good choice of ligand. The mathematical analysis for QSAR has aided in constructing ligand-target (L-T) and Li-T-Di (L-T-D) networks and in elucidating out the pharmacological effects too. Hence, through these methods, a new aspiration is emerging for the treatment of Osteoarthritis through the promiscuous effect of Rsk2 inhibitor and 2D-QSAR respectively.

Keywords: Rsk2, docking, QSAR, collagen, Phosphoaminophosphonic acid, Osteoarthritis

Chapter – 01

INTRODUCTION AND OBJECTIVE

1. Introduction and Objective

Osteoarthritis (OA), originating from the Greek words “bone”, “joint”, and “inflammation”, is one of the most common causes of pain and disability in middle-aged and older people. OA is currently considered an inflammatory disorder of movable joints that is involved in several pathological features such as deterioration and abrasion of articular cartilage and formation of new bone at the articular surface and subchondral bone, resulting in limitation of joint movement. The incidence of symptomatic OA is likely to increase because of the aging population and obesity epidemic. In the United States, the prevalence of OA of the knee is 10% in men and 13% in women in millions among adults 60 years of age or older in 2010. Radiographic evidence of OA generally appears in those over 65 years of age, approximately 80% of whom are over 75 years of age.

Osteoarthritis (OA) is a joint disease that mostly affects cartilage. The top layer of cartilage breaks down and wears away. This allows bones under the cartilage to rub together. The rubbing causes pain, swelling, and loss of motion of the joint. Different manifestations may incorporate joint swelling, diminished scope of movement. The most ordinarily included joints are those close to the closures of the fingers, at the base of the thumb, neck, lower back, knees, and hips. Joints on one side of the body are frequently more influenced than those on the other. Osteoarthritis occurs most often in older people. Younger people sometimes get osteoarthritis, primarily from joint injuries.

The principle side effect is torment, bringing about loss of capacity and frequently solidness. "Agony" is for the most part depicted as a blazing sensation in the related muscles and tendons. OA can bring about a crackling disturbance, when the influenced joint is moved or touched and individuals may experience muscle fits and withdrawals in the tendons. Sporadically, the joints might be loaded with fluid. Some individuals report expanded agony connected with icy temperature, high stickiness, and/or a drop in barometric weight, however studies have had mixed results. OA normally influences the hands, feet, spine, and the huge weight bearing

joints, for example, the hips and knees, As OA advances, the influenced joints seem bigger and solid. In littler joints, for example, at the fingers, hard augmentations, called Heberden's hubs (on the distal interphalangeal joints) and/or Bouchard's hubs (on the proximal interphalangeal joints), may shape, and however they are not so much difficult, they do restrict the development of the fingers essentially. OA at the toes prompts the arrangement of bunions, rendering them red or swollen. A few individuals see these physical changes before they encounter any torment. OA is the most widely recognized reason for a joint inflammation of the knee. Over expression of Rsk2 leads to this diseases Osteoarthritis.

Rsk2 an AGC kinase of the RSK family. Phosphorylated and activated by Erk1 and 2 in response to many growth factors, polypeptide hormones and neuro transmitters. Several phosphorylation sites are important for its activation. Possesses two kinase domains connected by a regulator linker region. Phosphorylates a wide range of substrates including ribosomal protein S6. Prominently expressed in brain structures essential for cognitive function and learning. In molecular biology, ribosomal s6 kinase is family of protein kinases involved in signal transduction. There are two sub families of RSK, one is p90rsk, also known as MAPK-activated protein kinase-1 (MAPKAP-K1), and another one is p70rsk, also known as S6-H1 Kinase or simply S6 Kinase. There are three variants of p90rsk in humans.

The MAPK/ERK pathway (also known as the RAS-RAF-MEK-ERK pathway) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell surface and ends when the DNA in the nucleus expresses a protein and produces some change in the cell, such as cell division. The pathway includes many proteins, including MAPK (mitogen-activated protein kinases, originally called ERK, extracellular signal-regulated kinases), which communicate by adding phosphate groups to a neighboring protein, which acts as an "on" or "off" switch. When one of the proteins in the pathway is mutated, it can become stuck in the "on" or "off" position, which is a necessary step in the development of many cancers. Components of the MAPK/ERK pathway were discovered when they were found in cancer cells. Drugs that reverse the "on" or "off" switch are being investigated as cancer treatments The main distinguishing feature between p90rsk and p70rsk is that the 90kDa family contain two non-identical kinase domains, while the 70kDa family contain only one kinase domain

Activated RAS activates the protein kinase activity of RAF kinase. RAF kinase phosphorylates and activates MEK (MEK1 and MEK2). MEK phosphorylates and activates a mitogen-activated protein kinase (MAPK). RAF, and MAPK are both serine/threonine-selective protein kinases. MEK (also known as MAPKK) is a tyrosine/threonine kinase. In the technical sense, RAF, MEK, and MAPK are all mitogen-activated kinases, as is MNK MAPK was originally called "extracellular signal-regulated kinases" (ERKs) and "microtubule-associated protein kinase" (MAPK). One of the first proteins known to be phosphorylated by ERK was a microtubule-associated protein (MAP). As discussed below, many additional targets for phosphorylation by MAPK were later found, and the protein was renamed "mitogen-activated protein kinase" (MAPK). The series of kinases from RAF to MEK to MAPK is an example of

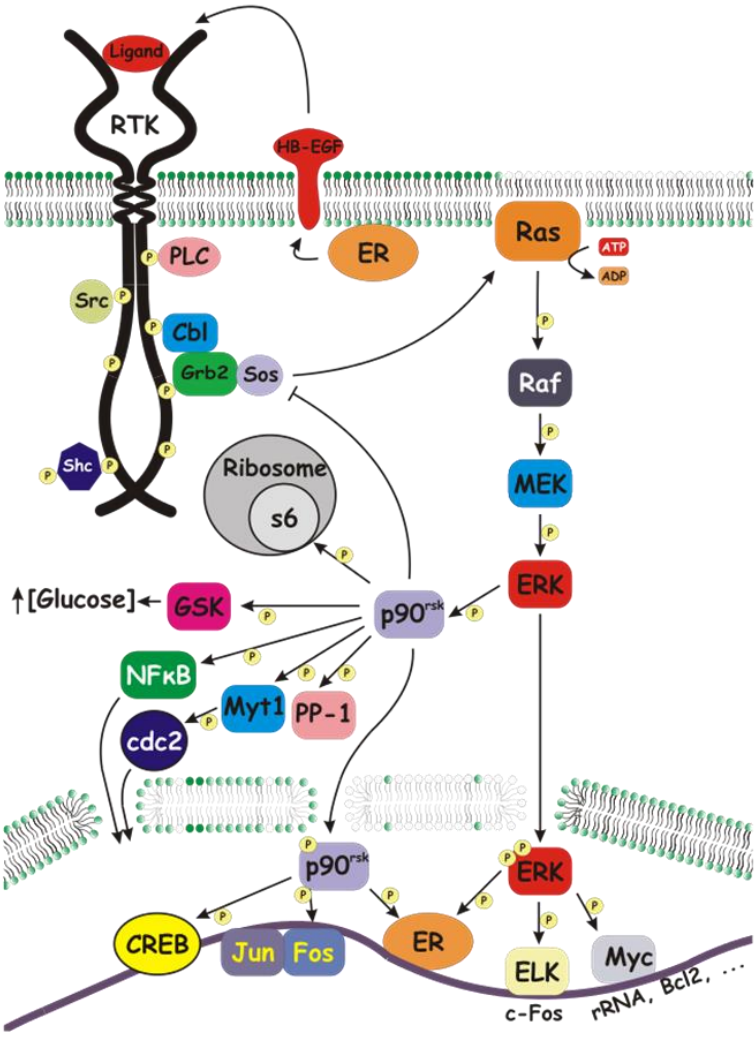

Figure 1 : MAPK/ERK pathway.

a protein kinase cascade. Such series of kinases provide opportunities for feedback regulation and signal amplification

1.1 Aim and Objectives of the Work

The aim of the work can be determined as follows:

- Designing novel lead molecules for osteoarthritis to cure the disease.

The objectives are as follows:

1. Finding the structure of RSK2 from 18 structure hits in PDB (Protein Data Bank).
2. Ligand binding site prediction.
3. Lead identification and optimization.
    - Ligand based docking in V Life Mds.
    - QSAR and analysis of models using V Life Mds.

Chapter - 02

LITERATURE REVIEW

2. Literature Review

The 90 kDa ribosomal S6 kinase 2 (Rsk2) is a serine/threonine kinase and is linked with the RSK family, which has N-terminal kinase space (NTKD) and a C-terminal kinase area (CTKD) associated by a linker region. Presently, Rsk2 has been confirmed to be a promising growth remedial tool because of its essential exhibitions in the regulation of cell process, for example, cell change, expansion and invasion. Moreover, over expression of Rsk2 is identified with numerous human diseases including breast cancer, prostate disease, Coffin-Lowry Syndrome and some hematopoietic stem cell carcinoma. Hence, these studies require a need of creating novel and powerful RSK2 inhibitors [1].

The p90 Ribosomal S6 kinases (RSK) are a family of 4 serine/threonine kinases widely expressed across tissues and activated in response to numerous hormones and growth factors. The RSK isoforms have a unique structure containing two non-identical kinase domains (N-terminal and C-terminal) that are separated by a linker region. A complex cascade of phosphorylation events is required for RSK activation. The current favored model for RSK activation entails ERK activating RSK's C-terminal kinase domain which then provides a phosphorylation-based docking site for PDK1 to bind and activate RSK's N-terminal kinase domain [4]. The N-terminal kinase then functions to phosphorylate numerous nuclear and cytoplasmic proteins that account for the ascribed cellular roles of RSK including cell survival, proliferation and motility. Its unusual activation scheme positions RSK to integrate signaling inputs from both the MAPK and PDK1 signaling pathways. Both of these pathways are relevant to oncology, as mutational activation of K-Ras and B-Raf are among the best validated oncogenic drivers of human cancers. In addition to this, tumor cell lines with these mutations also have strong phosphorylation of RSK activation sites, and recent publications account for mutationally activated FGFR as an additional cancer-relevant kinase that can phosphorylate RSK.

At present, many strong Rsk2 inhibitors have been accounted, among them, SL0101 is the initially reported particular inhibitor of Rsk2, which was removed from the tropical plant "Forsteronia refracta" demonstrated an IC50 estimation of 89 nM. Some established protein kinase inhibitors are likewise discovered to be dynamic yet nonspecific against Rsk2, for example, PKC inhibitors GF109203X and Ro31–8220 which may give valuable data to create Rsk2 inhibitors. Nowadays, Fmk is an inhibitor intended to irreversibly bind to the CTKD of Rsk2 and shows strong restraint with an IC50 of 15 nM. However, just two precious stone structures of Rsk2 NTKD complexed with comparative inhibitors have been discharged recently [1]

Thus, efficient Rsk2 inhibitor should be developed to incorporate clinical applicability. Rsk2 comprises of two non-indistinguishable kinase spaces, each with its own particular ATP-binding site. The N-terminal area (NTD) is p70 S6 kinase (p70 S6K), protein kinase C (PKC), while the C-terminal area is like calcium/calmodulin protein kinases. Two pyrrolo pyrimidine subsidiaries have been accounted for being counted as irreversible inhibitors of Rsk2. Ro31-8220 18 and GF109203X 2,9 are two bisindole-maleimides of PKC and Rsk2 inhibitors respectively. with IC50's of 36 and 310 nM, respectively [2]. Since the Rsk2 exhibits a three dimensional structure, hence this study helps in developing a nuclear model of RSK2 (buildups 68– 323) which was eventually utilized to recognize two novel Rsk2 NTD inhibitors from the National Cancer Institute (NCI) open substance archive. At present, new technology has come into limelight for enhancing the efficiency and importance of drug discovery. The research domain in China focuses on the recent trend of the scientific advances, have provided various inventions and among this Computational Drug Discovery and Design, which is gaining importance nowadays. The scientists have laid down the techniques for computational approach that includes target prediction and drug repositioning approaches, docking and scoring algorithms, virtual screening and lead optimization techniques. It was also reported that the design of the hybrid drug aims to circumvent the drug resistance, minimize the risk of drug interactions, counterbalance the known side effects associated with the other hybrid part and amplify the activity through the interaction with multiple targets as one single molecule [5]. In the last few years, hybrid drug design has emerged as a prime tool for the discovery of innovative anticancer therapies that can potentially overcome most of the pharmacokinetic drawbacks encountered when using conventional anticancer drugs [5].

Chapter - 03

METHODOLOGY

3. Methodology

3.1 Software used:

Argus Lab

Pymol

Open babel

V Life Mds

3.1 File formats used:

PDB file format

SDF file format

SYBYL MOL2 file format

3.2 Methods / Processes:

Protein structure retrieval in Argus lab.

Molecular docking of protein Rsk2 with ligands.

Inhibitor based QSAR study of protein Rsk2.

Protein structure retrieval in Argus lab:

The three dimensional structure of target protein was retrieved from PDB (Protein Data Bank; http://www.rcsb.org/pdb/). Miscellaneous ligands and other hetero-atoms like water, ions were removed from the protein models for active site predictions and further docking studies using vLife MDS.

The protein structure of Rsk2 which is in complex with afzelin with pdb Id 4EL9 was downloaded from PDB (Protein Data Bank; http://www.rcsb.org/pdb/) in PDB format.

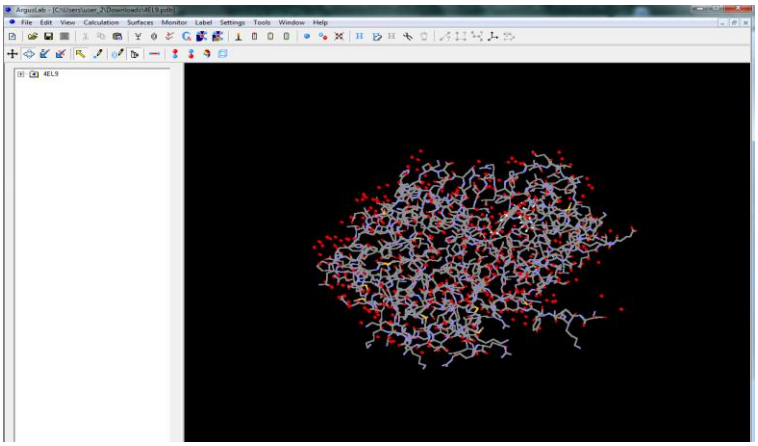

Figure 2: Structure of Rsk2 with afzelin

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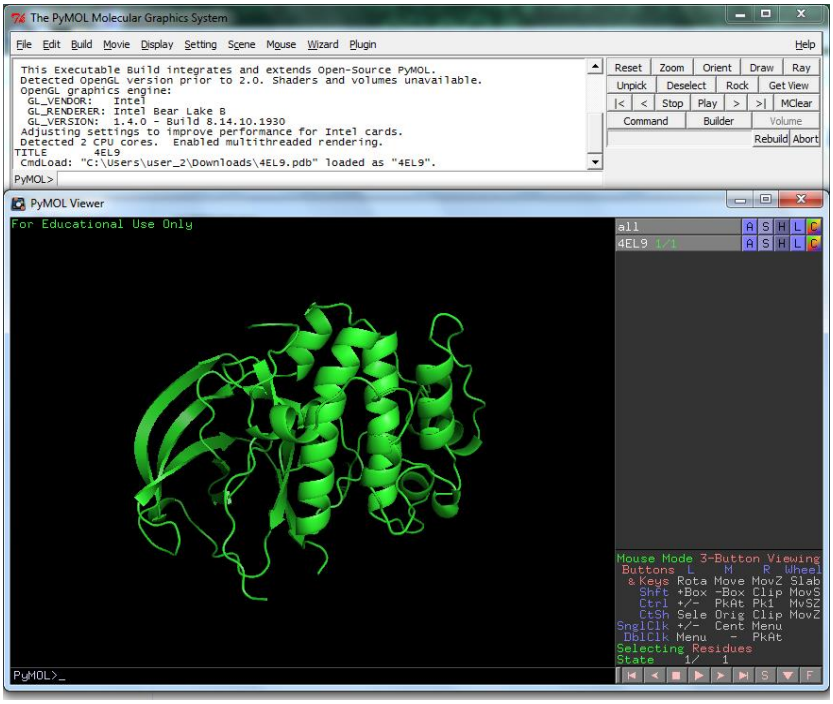
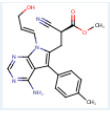


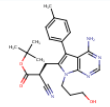
Figure 3: Structure of Rsk2 without any ligand:

Retreieval of ligand molecules:

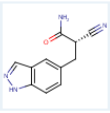
After preparing the protein structure in Argus Lab, we identified 19 ligand hits from PDB (Protein Data Bank). All these are downloaded in SDF file format from PDB. Then their format was changed in to MOL2 by open babel software for docking analysis by vLife MDS.



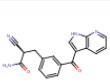
Name: methyl (2S)-3-{4-amino-7-[(1E)-3-hydroxyprop-1-en-1-yl]-5-(4-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl}-2-cyanopropanoate
ID: 0JG 1 Structure Containing 0JG (4D9T) (1 Structure in current Structure Hits)
Formula: $C_{21}H_{21}N_5O_3$



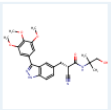
Name: tert-butyl (2S)-3-[4-amino-7-(3-hydroxypropyl)-5-(4-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-2-cyanopropanoate
ID: 0JH 1 Structure Containing 0JH (4D9U) (1 Structure in current Structure Hits)
Formula: $C_{24}H_{29}N_5O_3$



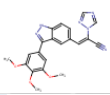
Name: (2S)-2-cyano-3-(1H-indazol-5-yl)propanamide
ID: 1LB 1 Structure Containing 1LB (4JG6) (1 Structure in current Structure Hits)
Formula: $C_{11}H_{10}N_4O$



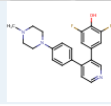
Name: (2R)-2-cyano-3-[3-(1H-pyrrolo[2,3-b]pyridin-3-ylcarbonyl)phenyl]propanamide
ID: 1LC 1 Structure Containing 1LC (4JG7) (1 Structure in current Structure Hits)
Formula: $C_{18}H_{14}N_4O_2$



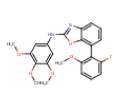
Name: (2S)-2-cyano-N-(1-hydroxy-2-methylpropan-2-yl)-3-[3-(3,4,5-trimethoxyphenyl)-1H-indazol-5-yl]propanamide
ID: 1LE 1 Structure Containing 1LE (4JG8) (1 Structure in current Structure Hits)
Formula: $C_{24}H_{28}N_4O_5$



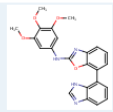
Name: (2Z)-2-(1H-1,2,4-triazol-1-yl)-3-[3-(3,4,5-trimethoxyphenyl)-1H-indazol-5-yl]prop-2-enenitrile
ID: 28D 1 Structure Containing 28D (4MAO) (1 Structure in current Structure Hits)
Formula: $C_{21}H_{18}N_6O_3$



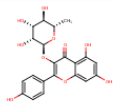
Name: 2,6-difluoro-4-{4-[4-(4-methylpiperazin-1-yl)phenyl]pyridin-3-yl}phenol
ID: 2NK 1 Structure Containing 2NK (4NUS) (1 Structure in current Structure Hits)
Formula: $C_{22}H_{21}F_2N_3O$



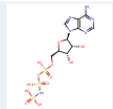
Name: 7-(2-fluoro-6-methoxyphenyl)-N-(3,4,5-trimethoxyphenyl)-1,3-benzoxazol-2-amine
ID: 2NR 1 Structure Containing 2NR (4NW5) (1 Structure in current Structure Hits)
Formula: $C_{23}H_{21}FN_2O_5$



Name: 7-(1H-benzimidazol-7-yl)-N-(3,4,5-trimethoxyphenyl)-1,3-benzoxazol-2-amine
ID: 2NS 1 Structure Containing 2NS (4NW6) (1 Structure in current Structure Hits)
Formula: $C_{23}H_{20}N_4O_4$



Name: 5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl 6-deoxy-alpha-L-mannopyranoside
ID: AFE 1 Structure Containing AFE (4EL9) (1 Structure in current Structure Hits)
Formula: $C_{21}H_{20}O_{10}$



Name: PHOSPHOAMINOPHOSPHONIC ACID-ADENYLATE ESTER
ID: ANP 537 Structures Containing ANP (1AD5, 1ANK, 1B63...) (1 Structure in current Structure Hits)
Formula: $C_{10}H_{17}N_6O_{12}P_3$

Ca^{2+}

Name: CALCIUM ION
ID: CA 8122 Structures Containing CA (158D, 196D, 1A0J...) (1 Structure in current Structure Hits)
Formula: Ca

Figure 4: Details of ligands.

Molecular docking:

Docking is used to predict the binding orientation of small drug like molecules to their protein targets, in order to predict the affinity of the small molecules. Hence, docking plays an important role in the rational design of drugs.

The computational docking of Rsk2 with ligand molecules were performed into the active site of corresponding protein models using vLife MDS software. Genetic algorithm (used in VLife MDS) offers a successful approach for globally inspecting the docked conformer's space. Genetic algorithms allow a population of solutions to prevail and in each generation. Difference of good or bad docked conformation is based on scoring function, which uses fitness functions on only electrostatic and both steric and electrostatic interactions between receptor-ligand as well as Dock score scoring function. The Dock score is also called as binding affinity of a given protein ligand complex with known 3-D structure. Dock score function include terms for van der Walls interaction, hydrogen bonding, hydrophobic effects.

Inhibitor based QSAR study of protein Rsk2:

Then after docking we performed QSAR (Quantitative Structure Activity Relationship) which analyses the relationship between molecular structure and biological activity. This makes a correlation between various molecular properties of a set of molecules with their experimentally known biological activity.

The process is elaborated below

1. For performing QSAR we identified common structure of the ligands. From literature review we identified 14 inhibitor molecules from reported article.
2. The structures of the compounds were built using molecular sketching window provided in vlife engine and structures for 2D QSAR study.
3. Energy minimization and batch optimization was carried out using Merck Molecular force field.
4. All the molecules were initially optimized and then used for the calculation of descriptors and further QSAR study.
5. All the 2D descriptors (thermodynamic, topological parameters) were calculated for QSAR analysis using vlife MDS software. Thermodynamic parameters describe free energy change during drug receptor complex.
6. The regression method is in the form of mathematical equation. This equation explains the variation of dependent variable with independent variable.
7. The QSAR model is used to predict the activity of new molecules for which the activity is not known.
8. The regression method which we used for generating QSAR model is PCR (Principal Component Regression).
9. The training set and test set is divided by sphere exclusion method.

2-Amino-7-substituted benzoxazole analogs were identified as potent inhibitors of Rsk2.

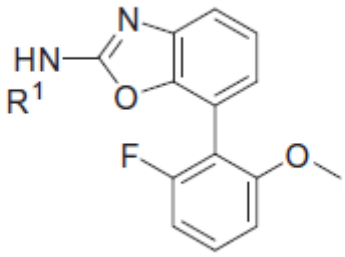


Figure 5: 2-Amino-7-substituted benzoxazole analog

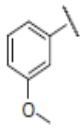
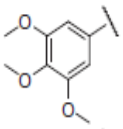
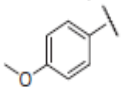
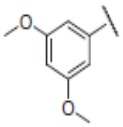
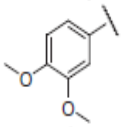
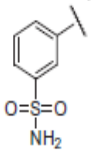
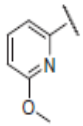
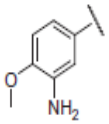
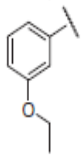
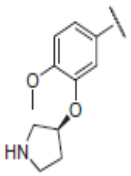
Compound	R^1	RSK2 IC_{50} (μM)	p-YB1 TM (μM)	Compound	R^1	**RSK2 IC_{50} (μM)**	p-YB1 TM (μM)
1		0.41	15.4	**8**		0.02	2.6
2	H	2.8	>20	**9**		1.4	>20
3		1.0	>20	**10**		0.21	17.2
4		0.62	>20	**11**		0.07	6.5
5		3.2	>20	**12**		0.34	>20
6		0.62	>20	**13**		0.22	>20
7		0.73	>20	**14**		0.01	6.3

Figure 6: IC 50 values of the potent inhibitors.

IC50:

The half maximal inhibitory concentration (IC50) is a measure of the effectiveness of a substance is inhibiting a specific biological or biochemical function. The IC50 value is considered as a dependent variable and descriptors which were calculated using 2D QSAR are considered as independent variables. The IC50 values of corresponding inhibitor molecules are converted in to log values.

IC50 is the drug concentration causing 50% inhibition of the desired activity. Strictly speaking, IC50 only causes inhibition of a specific individual target, e.g. inhibition of an isolated enzyme, or reduction in fluorescence for a luciferase reporter assay for an individual protein of interest, etc.

Chapter – 04

RESULTS AND DISCUSSION

4. Results and discussion

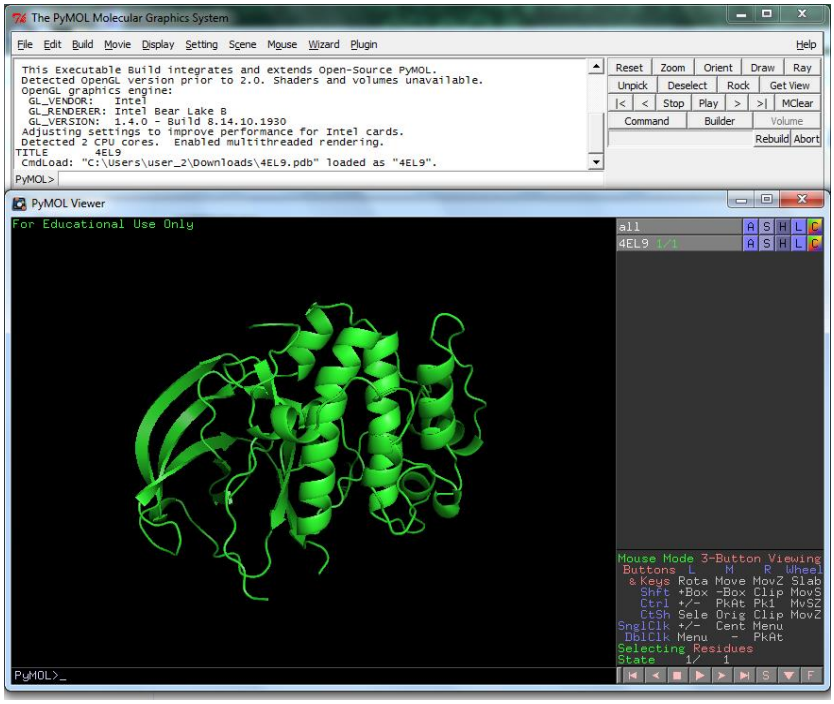


Figure 7: structure of RSK2

4.1 Docking results:

We have choosen total 19 ligands out of which 10 ligands docked properly and their minimum binding energy is given as docking score.

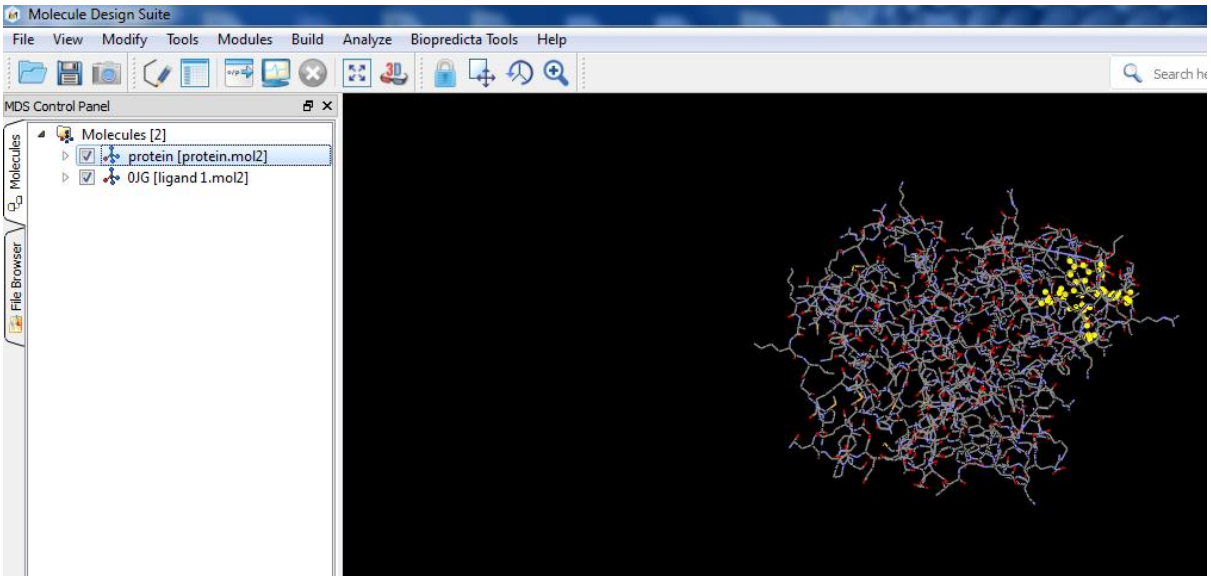


Figure 8: Docking complex with ligand 1 (0JG)

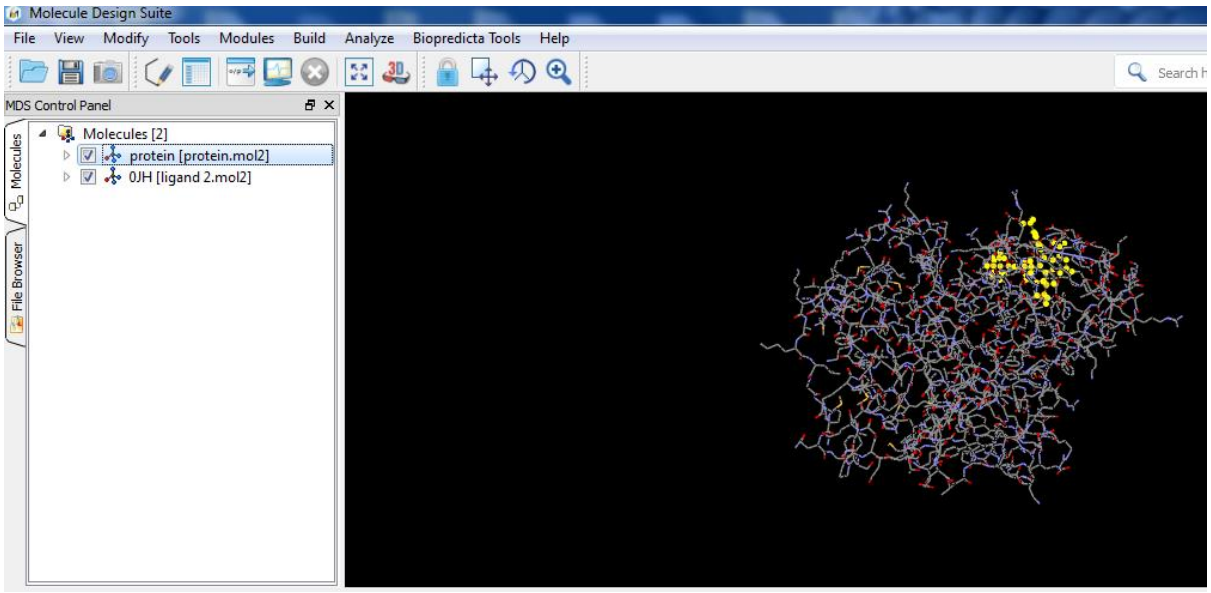


Figure 9: Docking complex with ligand 2 (0JH)

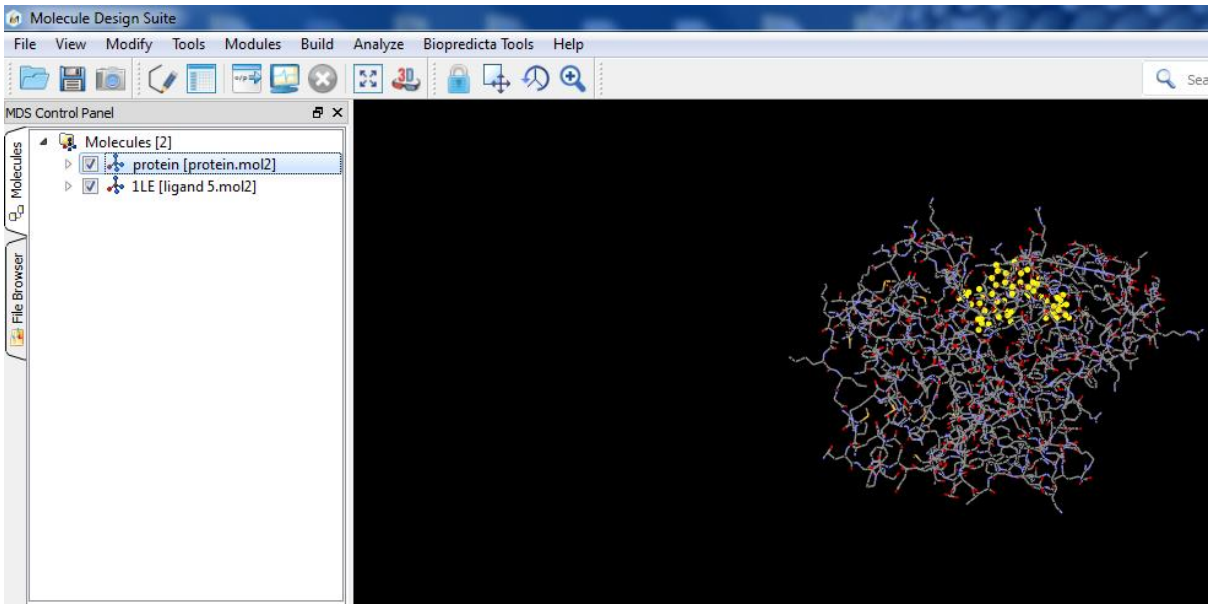


Figure 10: Docking complex with ligand 5 (1LE)

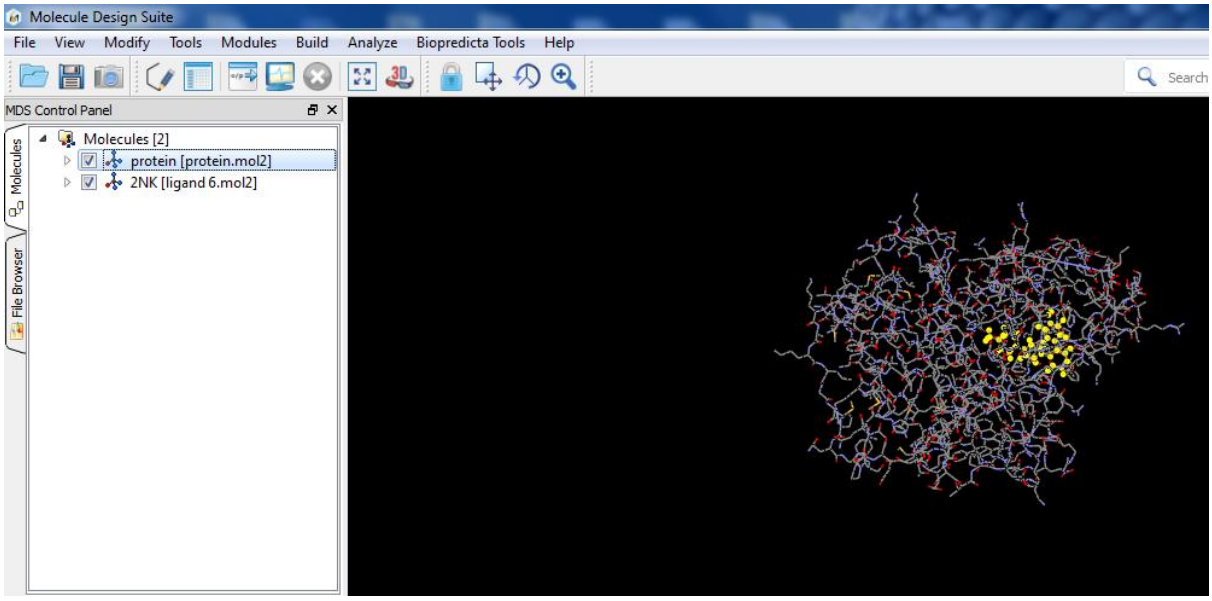


Figure 11: Docking complex with ligand 6 (2NK)

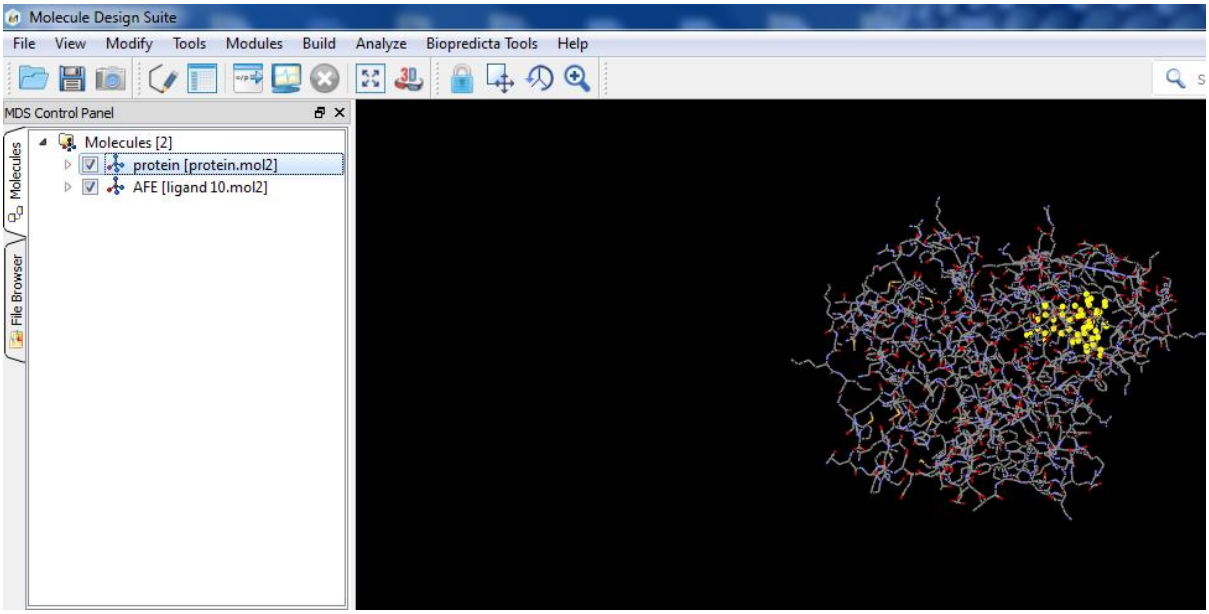


Figure 12: Docking complex with ligand 10 (AFE)

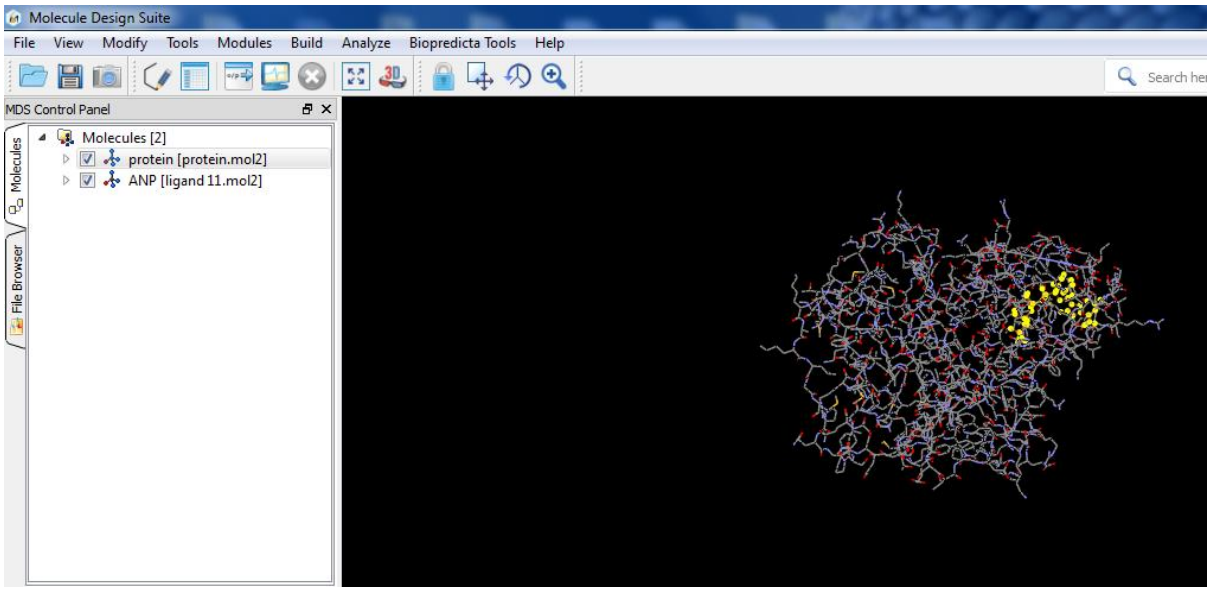


Figure 13: Docking complex with ligand 11 (ANP)

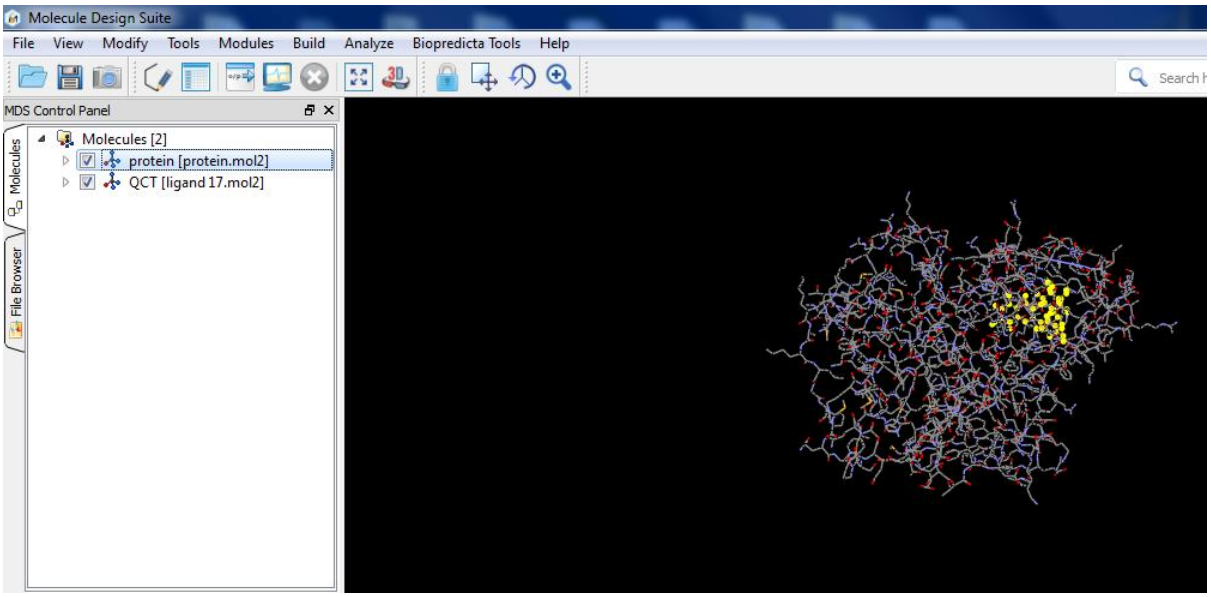


Figure 14: Docking complex with ligand 17 (QCT)

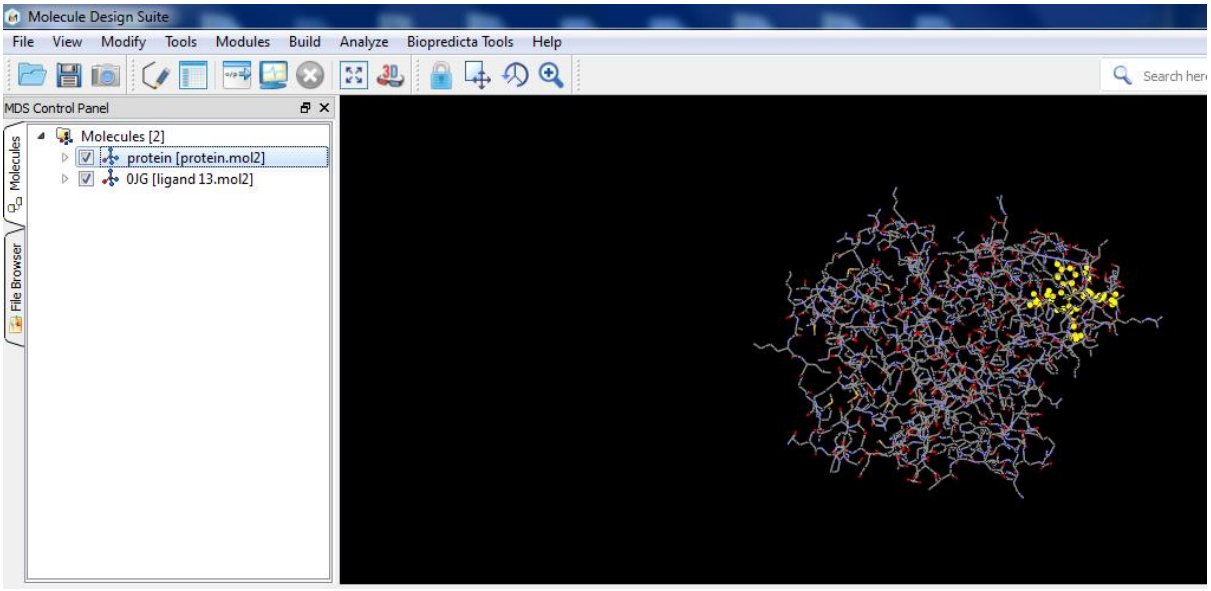


Figure 15: Docking complex with ligand 13 (0JG)

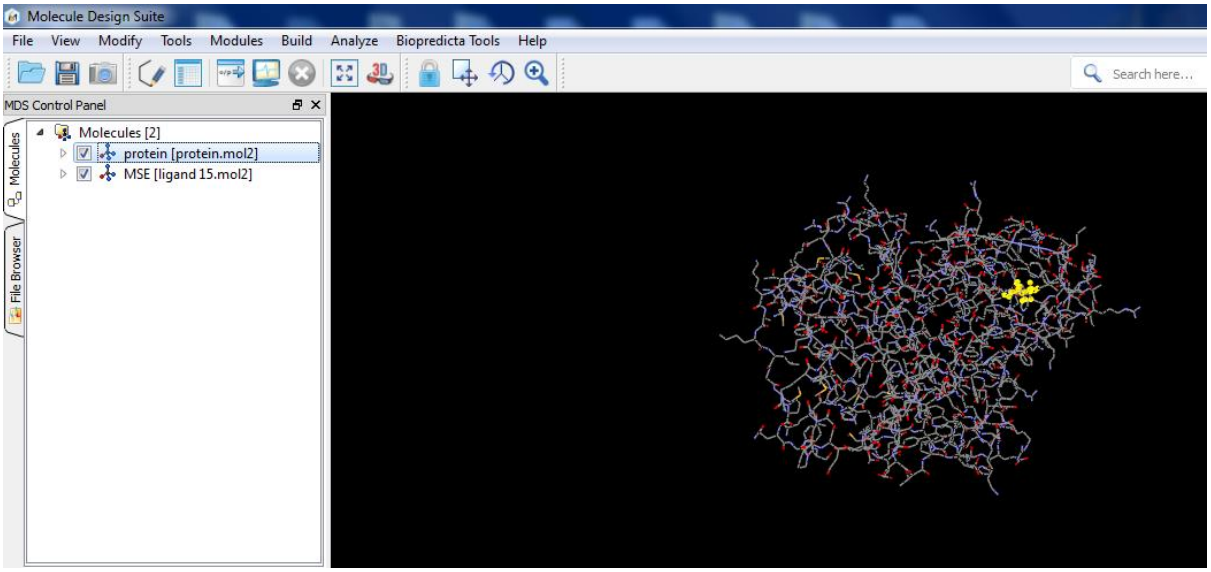


Figure 16: Docking complex with ligand 15 (MSE)

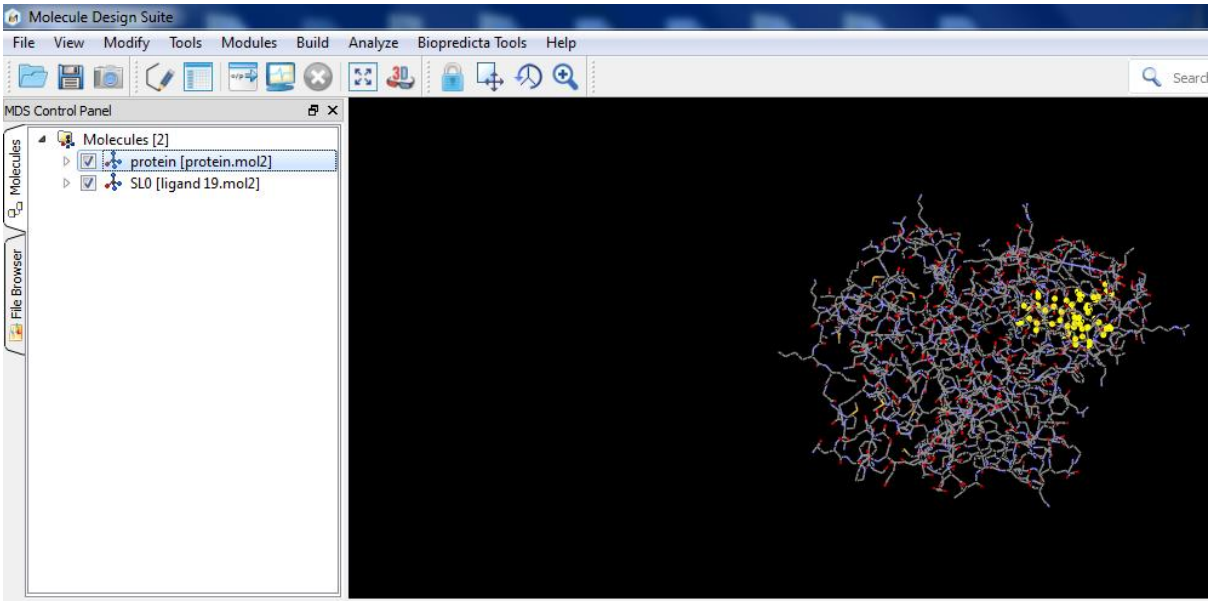


Figure 17: Docking complex with ligand 19 (SL0)

Ligands PDB id	Docking score	Docking status
0JG	-3.895584	DOCKED
0JH	-3.895584	DOCKED
1LC	-3.895584	DOCKED
1LE	-3.895584	DOCKED
2NK	-3.895584	DOCKED
AFE	-3.895584	DOCKED
ANP	-4.036595	DOCKED
MSE	-3.895584	DOCKED
QCT	-3.895584	DOCKED
SLO	-3.895584	DOCKED

Table 1: ligand PDB ids with dock scores

From the above table docking of the ligands was carefully observed and their interactions and orientations were also monitored. The results show that Phospho Amino Phosphonic Acid (Pdb id ANP) having a highest binding affinity with dock score -4.036595.

4.2 QSAR results:

Quantitative Structure-Activity Relationship (QSAR) is used to build mathematical models for bioactivity prediction. Any QSAR model for given set of molecules correlates the activities with properties inherent to each molecule in the set itself. 14 inhibitor compounds with known IC50 values were used to generate independent training and test data sets. Initially, all 9 compounds were clustered and defined as training sets, and other 5 compounds are considered as test set.

Training set and test set descriptors, generated by sphere exclusion method vLife MDS software usues PCR(Prinicipal Component Regression) method to construct and cross validate the QSAR model. QSAR model equation with best score (q2) .and correlation (r2) value of the fits were reported (Table). The QSAR model equation was validated with experimental IC50 values of training set and then, used for the prediction of activities of test set compounds.

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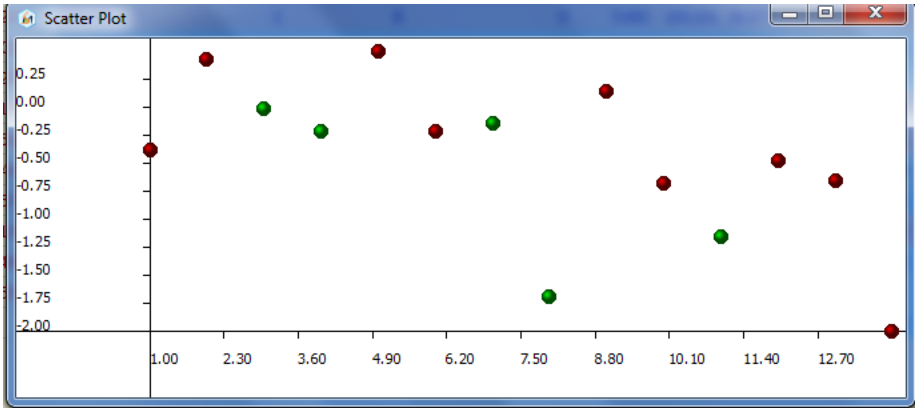

Figure 18: Activity distribution plot of training set and test set

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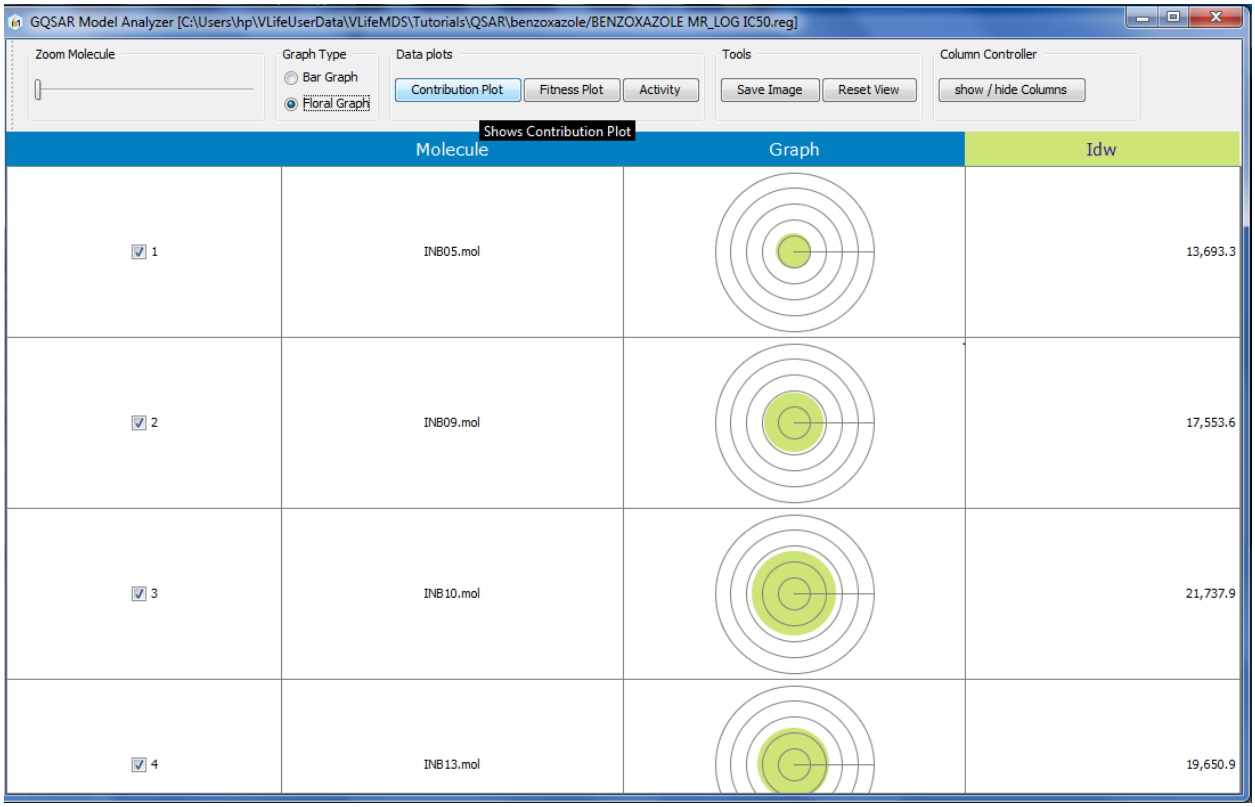

Figure 19 : The floral graph which depicts the value of descriptors

PARAMETERS	DESCRIPTION	RESULTS
n	number of molecules	14
df	degree of freedom (n-k-1) higher is better	7
r2	coefficient of determination (> 0.7)	0.8655
q2	cross validated r2 (> 0.5)	0.6854
pred r2	r2 for external test sets (> 0.5)	0.5663
F- test	F- test for statistical significance of the model (higher is better)	45.0286

Table 2: QSAR parameter's results.

The fitness plot between the training sets and test sets is shown below. All the test set and training set molecules should be near to regression line.

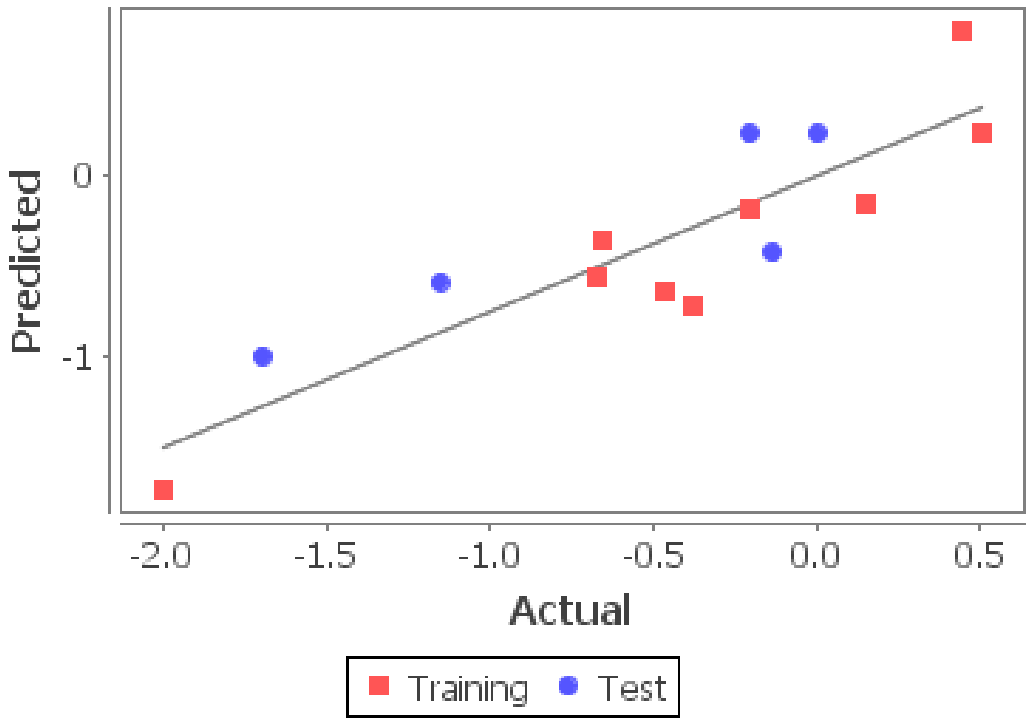

Figure 20: Fitness plot between actual and predicted values

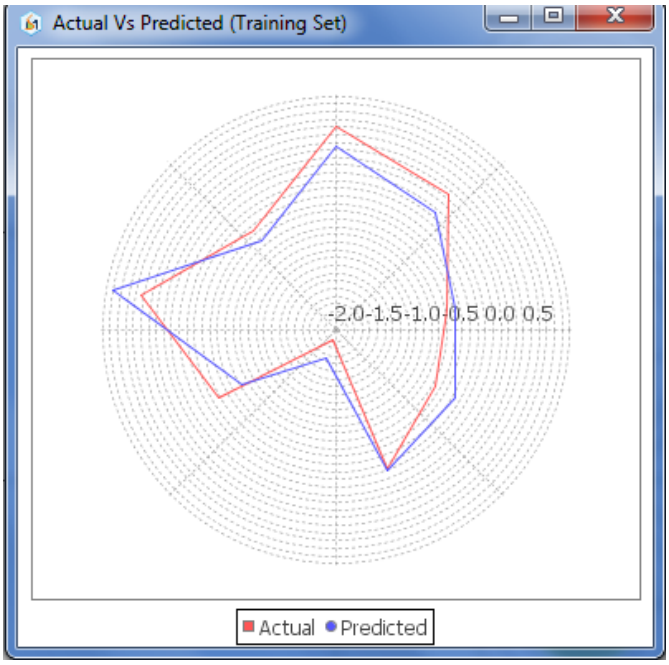

Figure 21: The actual vs predicted conformation of training sets.

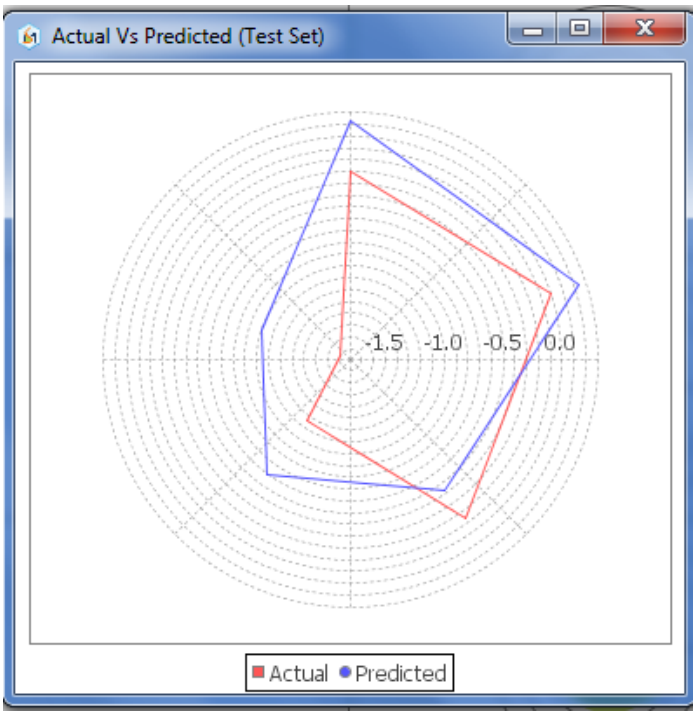

Figure 22: The actual vs predicted conformation of test sets.

Chapter - 05

SUMMARY AND CONCLUSION

4. Summary and Conclusion

The interaction between the ligand molecules and the protein was analyzed using docking studies by vlife MDS. From these results we can say that the best one is the result of ANP. 14 experimentally characterized benzoxazole aniline as Rsk2 inhibitors were obtained from literature. Their structure-activity relationship was calculated using pharmacophore based 2D-QSAR method by taking 9 inhibitor molecules as training set . The developed 2D-QSAR model was validated with a test set consists of 5 molecules. The results obtained from QSAR and docking studies suggest that the four different core regions of the inhibitor molecules differ in their activity and binding to the protein based on the substitutions upon the aromatic rings of the core. The favorable and infavorable regions for the interactions such as H-bonding, electrostatic and hydrophobic were identified. This information would help to design new poteintial inhibitors against Rsk2 proteins which are used to cure the osteroarthritus.

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