Identifying Structural Features of Sulforaphane Derivatives Based on QM Force Field for Predicting the Anti-Cancer Activity

Neena Elsa Eapen, Md Afroz Alam

Abstract: ***Sulforaphane (SFN) is a biologically active compound-based drug obtained from cruciferous vegetables, which has been investigated for its anti-tumor and chemopreventive effects. SFN shows a potential mechanism of its anti-cancer activity by binding to Macrophage Migration Inhibitory Factor (MIF) which is a pleiotropic cytokine that overexpresses in cancer cells increasing the aggressiveness of the disease. SFN can significantly inhibit the action of MIF on angiogenesis and the prevention of apoptosis in cancer cells. Preclinical studies on the anti-cancer activity of SFN showed promising results but in clinical studies, it is not yet convincing. Screening of a set of compounds chemically related to SFN can have a chance of showing promising anticancer activity. The quantitative structure activity relationship (QSAR) based on quantum mechanics has been done to derive the best mathematical model of these selected derivatives of sulforaphane for the calculation of its biological activity. These sulforaphane derivatives have been evaluated with respect to their ADMET and physicochemical properties. Validation was done to indicate the predictiveness of the model. The significant R^2 value of 0.5676 between experimental and predicted biological activity and R^2_{cv} value of 0.554 depicts a decent statistical fit of the model. A best QSAR model has been selected which has a future scope of helping in designing anti-cancerous drugs.***

Keywords**: Sulforaphane, MIF, Molecular docking, Binding affinity, QSAR, and ADMET properties.***

I. INTRODUCTION

The second leading cause of death is found to be cancer throughout the world. A healthy diet of vegetables prevents cancer as it contains phytochemicals [1]. Sulforaphane (SFN) is an isothiocyanate that is naturally obtained from cruciferous vegetables for example cabbage, broccoli, and kale. Fig. 1 shows its synthesis in the human body [2].

SFN is extensively accepted as a chemopreventive agent because it has an effect of regulation on apoptosis, tumor cell cycle and angiogenesis [3]. Some of the apoptotic pathways are induced and some other angiogenic pathways are inhibited by SFN. One among them is the inhibition of the macrophage migration inhibitory factor (MIF). Recently, many studies have revealed that tumors have been associated with the overexpression of MIF and help in their progression by having an effect on invasiveness and cell proliferation [4].

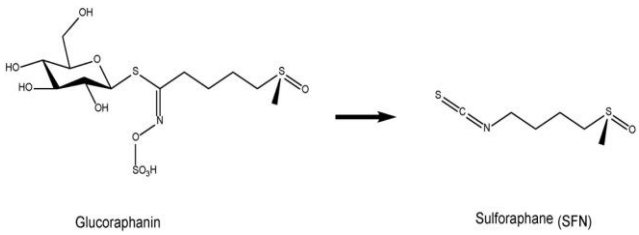

Fig. 1. Reaction scheme of the enzymatic (myrosinase) conversion of glucoraphanin to sulforaphane by gut bacteria in the gut

MIF effects in cancer take place primarily by its binding to the CD74 receptor that is present on the surface of cancer cells [5]. SFN found to be a potent inactivator of MIF tautomerase activity. MIF is a homotrimer that has two antiparallel α-helices and six β-pleated sheets in each subunit [6]. The catalytic base of MIF is the N-terminal proline of each subunit that resides in the hydrophobic pockets and has very low pKa values. These are extremely reactive with electrophiles like isothiocyanates [7]. Even though the anti-cancer activity of SFN has been widely explored and reported, there is a difficulty regarding the dose administration which leads to its significant limitation in clinical use. In human trials, there appeared a restriction in the bioavailability of the compound after administration and consumption. Consequently, this commercially available SFN supplement has not yet approved by the FDA for any treatment [8]. Therefore, screening of compounds chemically related to the compound sulforaphane i.e., the derivatives can have a chance of potential anti-cancer drug activity.

All the molecules can be analyzed in-silico for predicting drug-likeness, ADMET, and molecular properties [9]. The current study also represents the quantitative structure activity relationship (QSAR) based on quantum mechanics of sulforaphane derivatives which involves the derivation of a mathematical formula that relates the biological activities of these derivatives to their physical and chemical parameters. These parameters have a major effect on the drug's activity. QSAR is a major method in chemometrics that helps in medicinal chemistry and drug design.

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***** Correspondence Author
Neena Elsa Eapen, Pursuing M. Tech, Department of Biotechnology, Karunya Institute of Technology and Sciences, Coimbatore - Tamil Nadu, India.
Md Afroz Alam*, Assistant Professor, Department of Biotechnology, School of Agriculture and Biosciences, Karunya Institute of Technology and Sciences, Coimbatore – 641114, Tamil Nadu, India.
Email: afroz@karunya.edu, maarkzin@gmail.com

The biological activity of molecules can be correlated to their chemical and physical parameters. Quantum-chemical and molecular modeling techniques help in characterizing the reactivity and binding properties of the molecules [10]. Through the decent correlation obtained, it is found that the QSAR model can be used to screen molecules against cancer [11].

II. METHODOLOGY

A. Compound Library Preparation

45 compounds similar to the parent molecule sulforaphane were collected from PubChem [12]. The biological activity values (IC_{50}) of these compounds were also collected from PubChem. They are then tabulated as shown in Table I. The 2-dimensional structures of these compounds were created from the Simplified Molecular-Input Line-Entry System (SMILES) notation available in PubChem using the software ChemSketch (ACD/Labs, v8.17). These are then converted into its 3-dimensional structures using the same software. After optimization, they were saved in mol format [11].

Table- I: List of the parent molecule structure and its derivatives with the biological activity (IC_{50}) values [12].

Molecule	Canonical SMILES	IC_{50} (µM)
SFN	CS(=O)CCCCN=C=S	9.20
SFN_1	CCOCCOC(=O)C	4.30
SFN_2	CS(=O)CCCN=C=S	4.93
SFN_3	CS(=O)C=CCCN=C=S	52.11
SFN_4	C(CCN=C=S)CCF	0.25
SFN_5	CS(=O)CCCCCN=C=S	6.80
SFN_6	CS(=O)(=O)CCCCN=C=S	12.59
SFN_7	CS(=O)C=CCCN=C=S	0.40
SFN_8	CS(=O)CCCCN=C=S	19.60
SFN_9	CS(=O)CCCCN=C=S	9.77
SFN_10	CP(=O)(C)CCCCN=C=S	0.40
SFN_11	CS(=O)CCCCCN=C=S	9.62
SFN_12	CS(=O)CCCCCN=C=S	12.00
SFN_13	CC(COC)OC(=O)C	2.62
SFN_14	COCCOC	0.74
SFN_15	C=COCCCCO	40.08
SFN_16	C=CCN=C=S	12.30
SFN_17	C1=CC=C(C=C1)CCN=C=S	9.70
SFN_18	COC(=O)CCC(=O)OC	4.61
SFN_19	CCCCCN=C=S	41.50
SFN_20	CCCCN=C=S	231.4
SFN_21	CSCCCN=C=S	0.45
SFN_22	C(CCN=C=S)CN=C=S	1.88
SFN_23	CS(=O)CCCCCCN=C=S	5.70
SFN_24	CCS(=O)CCCCN=C=S	3.85
SFN_25	CS(=O)CCCCCCN=C=S	10.06
SFN_26	CC(C)S(=O)CCCCCN=C=S	3.42
SFN_27	CS(=O)CCCCCCN=C=S	7.54
SFN_28	CCS(=O)CCCCN=C=S	19.78
SFN_29	C(CCC=O)CCN=C=S	19.70
SFN_30	CCCS(=O)CCCCN=C=S	10.74
SFN_31	CCCCS(=O)CCCCN=C=S	9.56
SFN_32	CC(C)S(=O)CCCCN=C=S	10.41
SFN_33	CC(C)S(=O)CCCN=C=S	16.70
SFN_34	CCCCS(=O)CCCCN=C=S	9.77
SFN_35	CCCN=C=S	177.00
SFN_36	CC(C)S(=O)CCCCCCN=C=S	11.99
SFN_37	C(CCCO)CCN=C=S	4.40
SFN_38	C(CN=C=S)CN=C=S	1.84
SFN_39	CCO[Si](C)(C)N=C=S	2.25
SFN_40	CSCCCCN=C=S	21.00
SFN_41	CC(C)N=C=S	10.80
SFN_42	C=CCN=C=S	12.30
SFN_43	C1=CC=C(C=C1)CN=C=S	8.40
SFN_44	C1=CC=C(C=C1)CCN=C=S	17.50
SFN_45	COC1=CC=CC=C1N=C=S	0.57

B. ADMET Property Prediction

The 3D structures of the SFN derivatives in mol format were transferred to the Schrödinger (LLC, New York, Maestro suite, v8.5) software and the project table was prepared. Those 46 structures were then minimized including the parent molecule sulforaphane. The ligands were prepared using the LigPrep module of the Schrödinger software (OPLS 2005 force field). ADMET properties of these 46 compounds were determined using the QikProp module of the same Schrödinger Maestro suite. QikProp generates physically relevant descriptors like molecular weight, logP, number of hydrogen acceptors and number of hydrogen donors of each compound. The prediction of Lipinski's rule of five was done to evaluate their drug-likeness. All the compounds showed promising findings giving the rule of five as 0 [11].

C. QSAR Model based on QM Approach

The minimum energy conformations of all the compounds and quantum mechanics based structural properties were calculated, using the PM7 force field method, by extracting from the MOPAC (2016, Version: 19.234W) files. The descriptors were then shortlisted to heat of energy, total energy, electronic energy, dipole moment, core to core repulsion, molecular weight, ionization potential, GAP, HOMO, LUMO, COSMO area and volume [13]. Predicted biological activity (pIC_{50}) has been generated between the descriptors and the observed biological activity. The set of descriptors that would provide the statistically best QSAR model was adopted by doing the regression analysis for each combination with the activity values using the Minitab software (2017, Minitab, LLC, v18.1) [14]. Finally, linear regression coefficient (R^2) and model validation coefficient have been established. A good fit has $R^2 > 0.5$ which depicts an acceptable model [14].

D. Validation of The QSAR Model

Using the leave-one-group-out cross-validation method, which is an important statistical validation technique, the complexity of an equation and the predictiveness capability and reliability of the QSAR model was determined. Cross-validation helps in computing the accuracy of the modeling technique. On the basis of Prediction Error Sum of Squares (PRESS) and the sum of squares of deviation of the experimental values from their mean (SSY), the cross-validation regression coefficient (R^2_{cv}) was calculated and is given by (1).

$$R^2_{cv} = 1 - \frac{PRESS}{SSY} = 1 - \frac{\sum_{n=1}^{N}(y_{exp} - y_{pred})^2}{\sum_{n=1}^{N}(y_{exp} - \bar{y})^2} \quad (1)$$

Where y_{exp}, y_{pred}, and y are respectively experimental, predicted and mean values of the experimental activity of sulforaphane derivatives [14]. 7 compounds were removed to get the best regression coefficient.

III. RESULT AND DISCUSSION

A. ADMET Properties

The absorption, distribution, metabolism, excretion and toxicity properties of the parent molecule sulforaphane and its 45 derivatives were determined using the QikProp module of Schrodinger software (Table II). QikProp creates physically admissible descriptors to predict ADMET properties [11]. Some of the important predicted descriptors were octanol-water partition coefficient, $logP_{o/w}$ (-0.21 to 2.58); central nervous system (CNS) activity; the logarithm of the predicted blood/brain barrier partition coefficient, logBB (-0.78 to 0.53). The Lipinski's rule of five was 0 for all the 46 compounds, which shows that all the compounds have the ability to act as a drug.

Table- II: SFN derivatives showing QikProp result (MW – Molecular Weight; donorHB – Number of hydrogen bond donors; accptHB – Number of hydrogen bond acceptors)

Molecule	MW (mol)	donorHB	accptHB	logPo/w
SFN_13	132.16	0	3.7	0.93
SFN_21	147.25	0	3	2.05
SFN_28	191.31	0	6.5	0.94
SFN	177.28	0	6.5	0.53
SFN_37	159.25	1	4.2	1.57
SFN_30	205.33	0	6.5	1.34
SFN_31	219.36	0	6.5	1.73
SFN_32	205.33	0	6.5	1.26
SFN_18	146.14	0	4	0.38
SFN_40	161.28	0	3	2.45
SFN_44	163.24	0	2.5	2.58
SFN_20	115.19	0	2.5	1.73
SFN_14	90.12	0	3.4	-0.21
SFN_36	233.39	0	6.5	2.05
SFN_7	175.26	0	6.5	0.47
SFN_41	101.17	0	2.5	1.08
SFN_4	147.21	0	2.5	2.4
SFN_6	193.28	0	6.5	0.26
SFN_17	163.24	0	2.5	2.58
SFN_1	132.16	0	3.7	0.86
SFN_38	158.24	0	5	1.25
SFN_27	205.33	0	6.5	1.33
SFN_5	191.31	0	6.5	0.9
SFN_24	191.31	0	6.5	0.94
SFN_19	129.22	0	2.5	2.14
SFN_12	191.31	0	6.5	0.9
SFN_29	157.23	0	4.5	1.04
SFN_42	99.15	0	2.5	1.1
SFN_33	191.31	0	6.5	0.83
SFN_43	149.21	0	2.5	2.21
SFN_35	101.17	0	2.5	1.23
SFN_16	99.15	0	2.5	1.1
SFN_39	161.29	0	3.35	1.91
SFN_15	116.16	1	3.4	1.68
SFN_9	177.28	0	6.5	0.53
SFN_11	191.31	0	6.5	0.9
SFN_23	205.33	0	6.5	1.33
SFN_10	191.23	0	7.5	0.41
SFN_34	219.36	0	6.5	1.73
SFN_3	175.26	0	6.5	0.47
SFN_26	219.36	0	6.5	1.63
SFN_2	163.25	0	6.5	0.1
SFN_25	205.33	0	6.5	1.33
SFN_45	165.21	0	3.25	1.78
SFN_8	177.28	0	6.5	0.53
SFN_22	172.26	0	5	1.64

B. QSAR Modelling based on QM Approach

If the molecular descriptors are suitable to predict the biological activity (pIC_{50}) then it shows the success of QSAR studies. This work dealing with the study of QSAR on a set of 46 molecules of sulforaphane derivatives with its physicochemical parameters. Thus, it is intended to produce models that help in designing of new derivatives with increased efficacy in the future [15]. The Step-wise correlations were derived by the multiparametric regression analysis (by hit and trial method) which gave one best correlation of regression value greater than 0.5. In this series, the most significant QSAR model that has been obtained with the descriptors Molecular weight (Table I), and Electronic Energy, Dipole Moment, Ionization Potential, Gap as given in Table III, generated by Molecular Orbital Package (MOPAC) with PM7 force field [16].

Table-III: The molecular descriptor values of all the derivatives generated by MOPAC [16].

Molecule	EE (eV)	Dipole (Debye)	Ionization Potential (eV)	GAP (eV)
SFN	-8065.29	5.37	8.85	-8.16
SFN_1	-8064.31	3.95	10.17	-11.27
SFN_2	-6877.64	6.77	8.92	-8.33
SFN_3	-7635.25	4.97	8.83	-8.62
SFN_4	-7035.25	4.02	8.91	-8.44
SFN_5	-9296.24	7.91	8.81	-8.49
SFN_6	-9755.64	5.11	8.99	-8.51
SFN_7	-7563.26	4.66	8.72	-8.04
SFN_8	-8059.46	5.20	8.83	-8.58
SFN_9	-8076.29	5.68	8.75	-8.64
SFN_10	-9219.48	0.18	8.96	-8.48
SFN_11	-9279.70	7.32	8.81	-8.56
SFN_12	-9280.29	7.41	8.80	-8.58
SFN_13	-8361.50	3.49	10.03	-11.27
SFN_14	-4736.77	0.10	9.95	-11.81
SFN_15	-6486.71	1.87	9.38	-10.55
SFN_16	-3250.85	4.77	8.87	-8.48
SFN_17	-7984.24	4.84	8.85	-8.47
SFN_18	-9355.81	5.31	10.78	-11.59
SFN_19	-5653.49	5.01	8.83	-8.42
SFN_20	-4588.22	4.59	8.87	-8.31
SFN_21	-5475.64	5.49	8.76	-8.23
SFN_22	-7037.67	1.28	9.01	-8.01
SFN_23	-10565.08	5.83	8.72	-8.64
SFN_24	-9402.82	5.48	8.77	-8.64
SFN_25	-10561.84	5.83	8.72	-8.64
SFN_26	-12156.98	7.96	8.69	-8.31
SFN_27	-10551.91	5.42	8.74	-8.64
SFN_28	-9402.48	5.42	8.77	-8.64
SFN_29	-7667.94	2.73	8.88	-8.57
SFN_30	-10724.90	4.96	8.84	-8.43
SFN_31	-12301.64	5.22	8.84	-8.55
SFN_32	-10856.44	5.87	8.74	-8.64
SFN_33	-9554.75	7.53	8.82	-8.56
SFN_34	-12302.99	5.18	8.84	-8.50
SFN_35	-3584.34	5.29	8.78	-8.53
SFN_36	-13524.10	6.56	8.67	-8.61
SFN_37	-8093.19	3.99	8.83	-8.57
SFN_38	-6016.28	4.53	9.12	-8.20
SFN_39	-7082.01	5.90	8.58	-8.33
SFN_40	-6596.13	4.36	8.72	-8.35
SFN_41	-3667.01	5.56	8.75	-8.64
SFN_42	-3250.78	4.76	8.87	-8.48
SFN_43	-6824.65	5.68	8.69	-8.21
SFN_44	-7985.57	4.86	8.85	-8.49
SFN_45	-8553.62	4.78	8.46	-7.58

Predicted biological activity (pIC_{50}) value has been calculated by given equation (2) which is generated linearly by using Minitab statistical package. Among the 46 compounds, 7 were omitted to get a regression value greater than 0.5 (Table IV) by Leave-One-Out (LOO) method.

$$pIC_{50} = 12.36 + 0.000455 \times \text{Electronic energy} - 0.1118 \times \text{Dipole Moment} + 0.818 \times \text{Ionization Potential} + 0.0384 \times \text{Molecular Weight} - 0.223 \times \text{GAP} \quad (2)$$

Table- IV: Observed and predicted IC50 values of 39 molecules (eIC50 – observed IC50 in the form -logIC50; pIC50 – predicted IC50)

Molecule	EIC_{50} [-log (IC_{50})]	pIC_{50}	Error
SFN	-0.96	-0.77	0.20
SFN_1	-0.63	-0.56	0.07
SFN_2	-0.69	-0.82	-0.13
SFN_3	-0.83	-1.03	-0.20
SFN_4	-1.10	-0.70	0.40
SFN_7	-0.50	-0.67	-0.17
SFN_8	0.40	-0.01	-0.41
SFN_10	-0.98	-0.94	0.04
SFN_12	-1.08	-0.95	0.13
SFN_13	-0.42	-0.76	-0.34
SFN_14	0.13	-0.29	-0.42
SFN_15	-1.60	-1.03	0.57
SFN_16	-1.09	-1.42	-0.33
SFN_17	-0.99	-1.13	-0.15
SFN_18	-0.66	-0.19	0.47
SFN_19	-1.62	-1.43	0.19
SFN_20	-2.36	-1.43	0.94
SFN_21	-0.27	0.06	0.34
SFN_22	-0.76	-0.87	-0.12
SFN_24	-0.59	-0.81	-0.22
SFN_25	-1.00	-0.87	0.13
SFN_26	-0.88	-0.81	0.07
SFN_27	-1.30	-0.80	0.50
SFN_29	-1.29	-0.94	0.36
SFN_30	-1.03	-0.80	0.23
SFN_31	-0.98	-0.98	0.00
SFN_32	-1.02	-0.99	0.02
SFN_33	-1.22	-1.08	0.15
SFN_34	-0.99	-0.99	0.00
SFN_35	-2.25	-1.61	0.64
SFN_36	-1.08	-1.28	-0.20
SFN_37	-0.64	-1.24	-0.60
SFN_38	-0.26	-0.24	0.02

SFN_39	-1.32	-0.66	0.66
SFN_40	-1.03	-1.68	-0.65
SFN_42	-1.09	-1.42	-0.33
SFN_43	-0.92	-1.43	-0.50
SFN_44	-1.24	-1.13	0.11
SFN_45	-2.76	-1.83	0.93

During the step-wise regression analysis, this is the model that has given the best fit with the regression coefficient R^2=0.5676 which depicts a decent data fit as shown in Fig. 2.

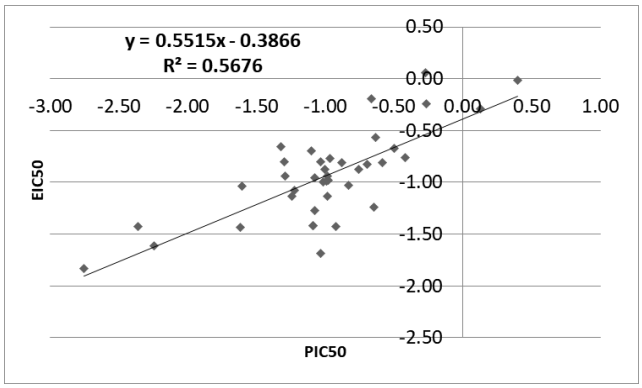

Fig. 2. Graph showing the regression coefficient of the best correlation of the QSAR model.

C. Cross-Validation

The cross-validation was carried out in which 7 molecules were removed from the set of 46 molecules and delivers the values of PRESS, SSY and R^2_{cv}. From this, the predictive power of the proposed model can be evaluated. PRESS has been asserted as a fair estimate of the error predicted by the model. If the PRESS/SSY is smaller than 0.4, the QSAR model can be considered reasonable [15]. The cross-validation regression coefficient for the best correlation obtained is as follows:

$$R^2_{cv} = 1 - \frac{PRESS}{SSY} = 1 - \frac{0.152}{0.341} = 1 - 0.45 = 0.554 \quad (3)$$

Using (3), the R^2_{cv} is obtained to be 0.554 (Table III). The cross-validated regression coefficient was found to be near to the R^2 value (0.5676) for the best correlation data set and thus this model can be accepted as statistically significant.

IV. CONCLUSION

The current work initiates with the compilation of a virtual library of sulforaphane analogues collected from chemical library. The set of derivatives were then predicted for the ADMET properties and found to have satisfying druggability from the obtained values of Lipinski's rule of five. A QSAR model based on the Quantum mechanics approach was developed and in a multivariate correlation, the physiochemical properties have shown significant regression value of greater than 0.5. The cross validation of the correlation has supported the result by getting a value near to the obtained regression value. The study thus illustrated that the QSAR model generated can be applied to guesstimate the biological activity for an assorted set of sulforaphane derivatives. The best developed QSAR model in terms of the druggability and activity relation has been selected over the parent molecule sulforaphane for designing anti-cancerous drugs may lead towards pharmaceutical development in future.

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AUTHORS PROFILE

Neena Elsa Eapen, I have completed B. Tech in Biotechnology from Sree Chitra Thirunal College of Engineering, Thiruvananthapuram, Kerala. My project in B.Tech entitled 'Larvicidal Activity of Synthesized Silver Nanoparticles Against Mosquito Larvae' which is based on the synthesis of silver nanoparticles from the leaf extract of Azadiracta indica (Neem). The synthesized silver nanoparticles are characterized by UV–vis spectrophotometer analysis and confirmation along with its particle diameter determination done by X-Ray Diffraction. The colloidal solution of these synthesized silver nanoparticles is then used against mosquito larvae to study its larvicidal property. I am currently pursuing my M.Tech in Biotechnology at Department of Biotechnology, Karunya Institute of Technology and Sciences, Coimbatore - Tamil Nadu. My focus is to develop a solution for current socially relevant problems which is being reflected by the research I did previously that has a scope on creating nanodrugs against mosquito vector and also the current work as it explains in this manuscript which has a scope of creating anti-cancerous drug.

Md. Afroz Alam, I have completed my Ph.D. in Bioinformatics. I am having 12 years of teaching and research experience with 20 publications in reputed Journals and 18 conference proceedings.

My research interest is in the rational designing of lead molecules based upon protein modeling and computational screening of small molecules (drugs) using both structure and free energy calculations of the drug-target docking models. I do this using various algorithms but particularly specialize in Molecular Mechanics-Generalized Born/Surface Area (MM-GB/SA), linear interaction energy models, and Pharmacophore generation) and ligand-based approaches such as, pharmacophore design, 2D-QSAR (quantitative structure activity relationship), 3D-QSAR, similarity searches. For the last seven years, I have been working on molecular modeling on the mechanisms of action and biological activity study of podophyllotoxin and Quanizoline based drugs. In this period of time, I have developed various models for the prediction of biological activity of podophyllotoxin and Quanizoline derived drugs. Research work also includes biological sequence analysis, important 3D and 4D protein structure feature extractions for accurate prediction modalities. The use of Artificial Neural Network, Support Vector Machine, Genetic algorithms based on pattern matching was very helpful for the functional annotation of raw linear sequences. Prediction of therapeutic targets using comparative genomics and comparative metabolomics and design of a candidate drug molecule against therapeutic targets was also an important component of my research area.

My project also involved extensive bench-based electrophoretic analyses of DNA fingerprinting. On the basis of my laboratory data, I performed further computational analyses such as RAPD, ISSR, SSR, AFLP, phylogenetic analysis. Then I combined chemical profiling of medicinal plants and finally mathematical modeling. Thus, my repertoire of basics is well suited to do extensive experience in successfully discovering new anti-cancer drugs and taking them from bench to bedside.