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Analysing QSAR Study of Quinolines Derivatives for their Cyotototoxicity Activity Against MCF-7 Cell Line

Anuradha Kumari

Department of Pharmaceutical Chemistry, School of Advanced Sciences, VIT University, Vellore, Tamil Nadu, India

Short Communication

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*For Correspondence

Anuradha Kumari, Department of Pharmaceutical Chemistry, School of Advanced Sciences, VIT University, Vellore, Tamil Nadu-632014, India; E-mail: annuradha26@gmail.com.

Keywords: QSAR, MCF-7 cell line, Quinolines, buildQSAR

ABSTRACT

Various quinolines and derivatives were characterized for anti-proliferative activity against MCF-7 cell line. MCF-7 is hormone inducing breast cancer cell line. QSAR (Quantitative Structural Activity Relationship) exerts to find persistent relationships among the variations in the values of molecular properties and the biological activity for a series of quinolone derivatives compound. Using the buildQSAR, Biological activity (IC50 value) was analysed with physicochemical properties such as Molecular weight, Hydrogen Bond Acceptor, Hydrogen Bond Donor, Log P, Log S of different quinolines derivatives against MCF-7 cell lines.

INTRODUCTION

Breast cancer is one of the most effective malignancies that occur either in one breast or can be in both. After lung cancer, breast cancer tops the list of tumour that is being depicted for the reason of death in woman. Around one among eight woman is being diagnosed with protruding breast cancer during thier life, and woman also have one in 33 fortunate chances of causing death from this disease. It is being predicted that 226,870 women will be dignified with and 39,510 women will die due to breast cancer in 2012. Substantial efforts have been attempted to create innovative approach for getting safe, productive and efficient methods to overcome breast cancer. By identifying various and different new target, more potent and novel therapeutic drugs have been identified and design for treatment of cancer. Various quinolines and derivatives were characterised for anti-proliferative activity against MCF-7 cell line. MCF-7 is a human breast adenocarcinoma cell line. As drug lead molecules increases down the reinforcement course, the ability to predict physicochemical, pharmacokinetic and toxicological properties of these lead molecules is becoming progressively important to reduce expense in developing new drugs and last moment development failure. Quantitative structure-activity relationship (QSAR) methods have lots to contribute in such areas.

QSAR is the quantitative correlation or relationship of the biological, pharmacological and toxicological activity to the structure of chemical entities that allows to predict drug efficacy of structurally similar entities. It also attempts to find uniform relationships among the variations in the values of physicochemical properties and the biological activity for number or series of homologus compounds such that it can be helpful for evaluating new drug entities.

A QSAR generally takes into account linear equation

$$\text{Biological Activity} = \text{Const} + (C1\ \ X1) + (C2\ \ X2) + (C3\ \ X3) + ...$$

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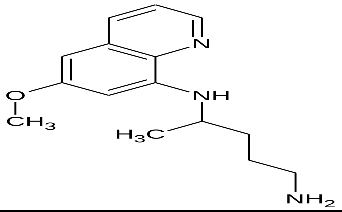
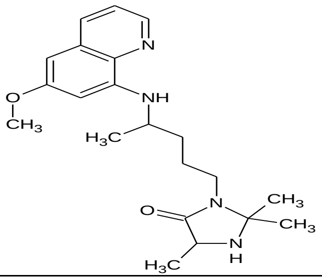
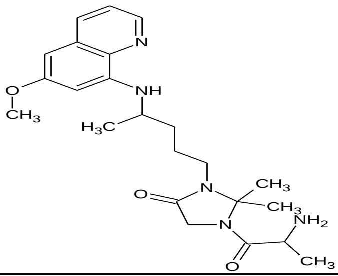
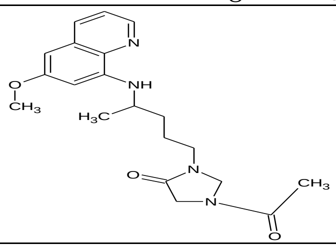
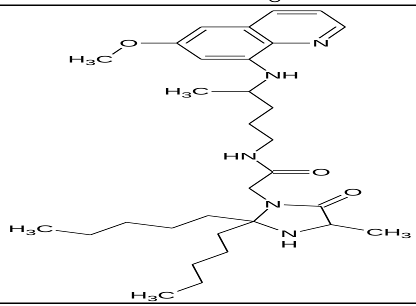
REVIEW: COMPUTATIONAL METHODS

Chemical Data

Different quinolines derivatives as MCF-7 cell line inhibitors were identified from the literature [3-25].

Table 1: List of Quinoline derivatives along with five descriptors.

S.no	Test Set	Molecular Weight	Hydrogen Bond Acceptor	Hydrogen Bond Donor	Log P	Log S
1		259.12	3	3	2.66	-2.87
2		369.24	3	2	3.28	-3.72
3		399.23	5	3	.05	-2.77
4		370.20	4	1	0.81	-2.44
5		539.38	5	3	5.53	-6.73

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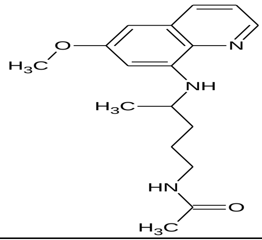
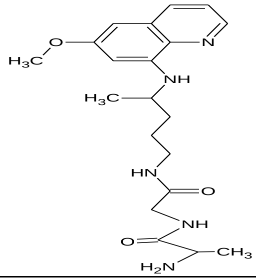
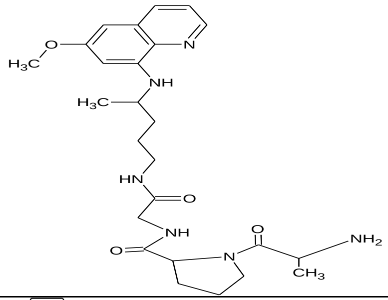
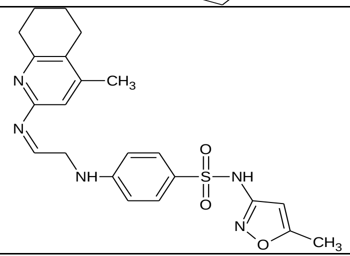
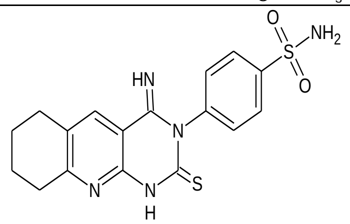
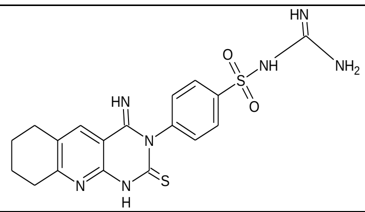
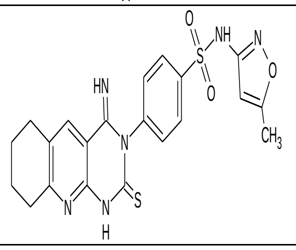
6		301.18	3	2	2.05	-2.66
7		387.23	5	5	0.35	-2.93
8		427.26	5	4	1.12	-3.70
9		449.15	6	2	4.32	-7.32
10		401.10	6	4	1.12	-5.68
11		443.12	6	6	0.99	-6.03
12		482.12	7	3	1.45	-5.91

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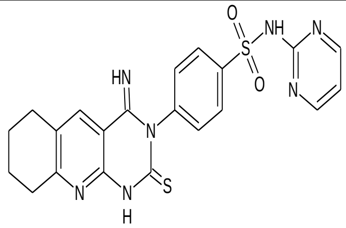
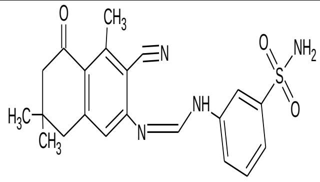
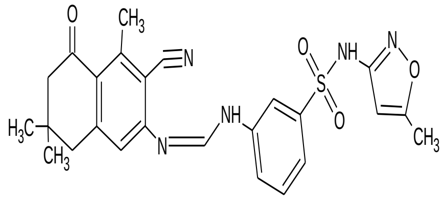
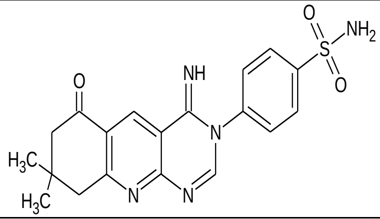
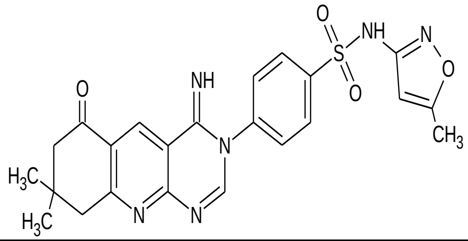
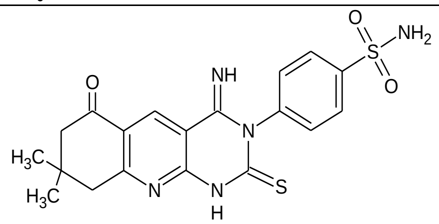
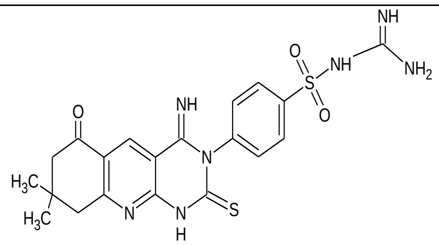
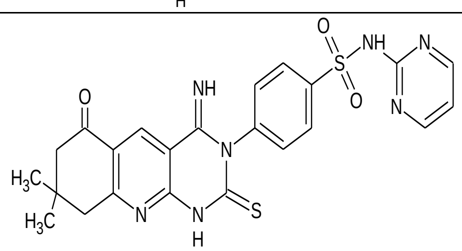
13		479.12	7	3	1.45	-5.91
14		411.14	7	3	1.58	-6.86
15		478.14	8	2	3.05	-7.18
16		411.14	7	3	1.16	-5.26
17		492.16	8	2	2.24	-6.14
18		443.11	7	4	0.71	-5.84
19		485.13	7	6	0.48	-6.19
20		521.13	8	3	0.94	-6.08

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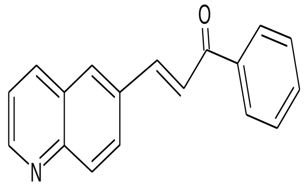
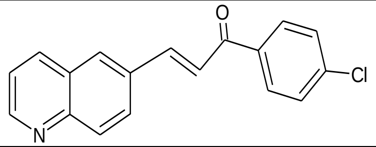
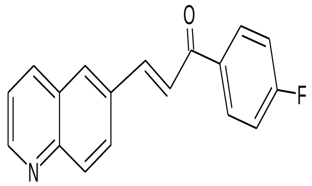
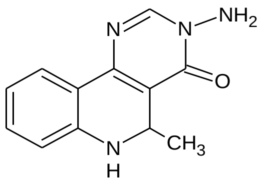
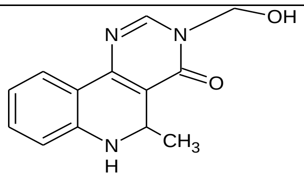
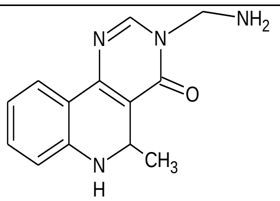
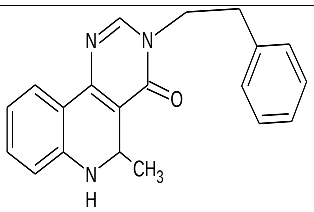
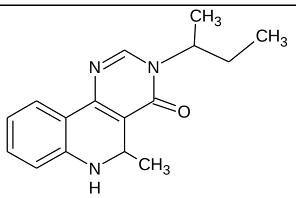
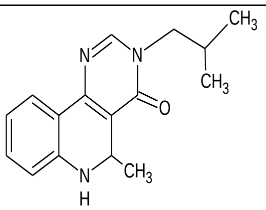
21		259.10	2	0	4.09	-5.18
22		293.06	2	0	4.77	-6.14
23		277.09	2	0	4.21	-5,70
24		226.09	4	2	1.16	-3.09
25		241.09	4	1	1.01	-2.79
26		240.10	4	2	1.18	-2.95
27		315.14	3	0	3.47	-4.55
28		267.14	3	0	2.95	-3.78
29		267.14	3	0	2.84	-3.61

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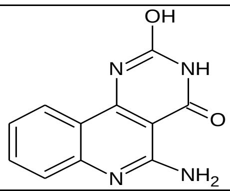
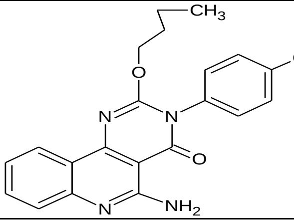
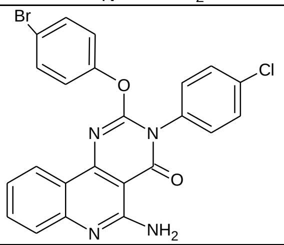
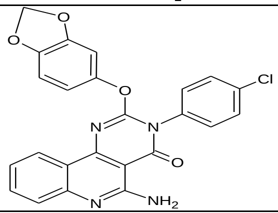
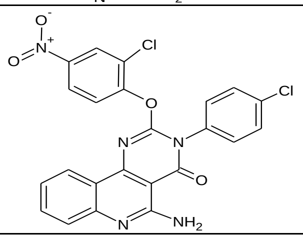
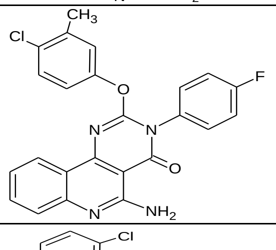
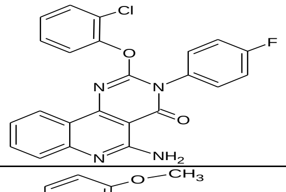
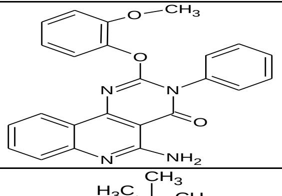
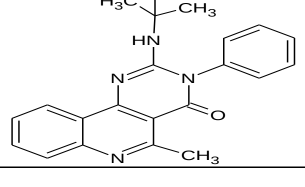
30		463.11	4	0	6.36	-8.03
31		443.10	5	0	4.82	-6.29
32		491.00	4	0	5.91	-7.60
33		457.08	6	0	4.92	-7.45
34		492.04	6	0	5.64	-7.73
35		445.10	4	0	5.63	-7.32
36		431.08	4	0	5.14	-6.48
37		409.14	5	0	4.13	-5.34
38		358.18	3	1	4.28	-4.55

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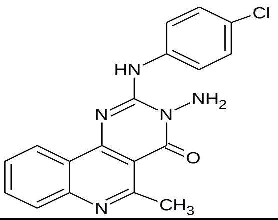
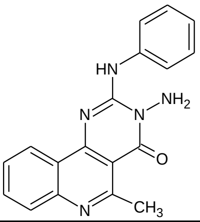
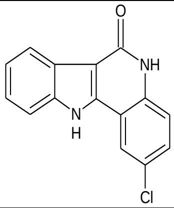
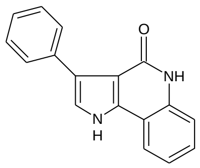
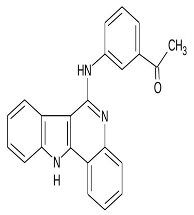
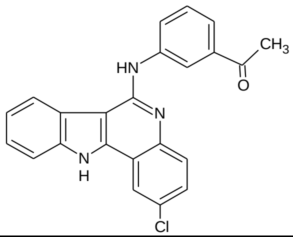
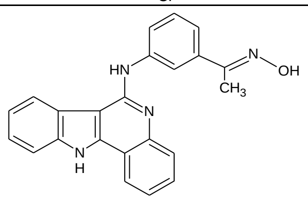
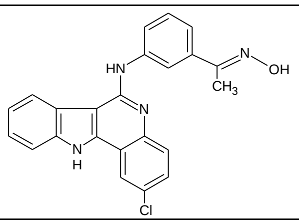
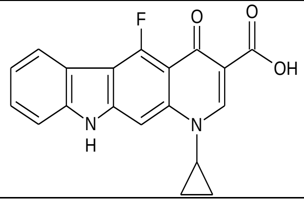
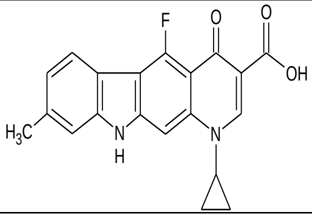
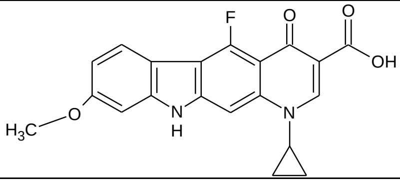
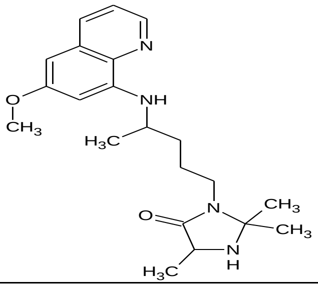
39		351.09	4	3	3.38	-4.96
40		317.13	4	3	2.69	-4.00
41		268.04	1	2	3.23	-5.84
42		260.09	1	2	3.09	-5.41
43		351.14	2	2	5.57	-6.73
44		385.10	2	2	6.36	-7.53
45		366.15	3	3	5.82	-6.92
46		400.11	3	3	6.47	-7.89

47		336.09	3	2	2.35	-5.64
48		350.11	3	2	2.78	-5.97
49		366.10	4	2	2.37	-5.79
50		427.26	5	3	1.55	-2.76

Biological Activity

Biological activity of different identified quinolines derivatives as MCF-7 cell line inhibitors were taken from reported literature [26-41] as IC_{50} values. IC_{50} concentration of drugs that is required for 50% of inhibition of MCF-7 cell lines as tabulated in table no. 1.

Molecular descriptors

Five molecular descriptors such as as Molecular weight(X1), Hydrogen Bond Acceptor(X2), Hydrogen Bond Donor(X3), Log P(X4), Log S(X5) was calculated from molsoft-molecules in silico software as tabulated in table no.1

METHODS

QSAR study by Multiple Linear Regression Analysis (MLR)

For QSAR studies, descriptors taken should be 1/10th of the molecules analysed as it will give good results and moreover compounds taken should be homologus [42-63]. Fifty different quinolines derivatives with five different descriptors were taken for study. All the descriptors are independent variables and biological activity is dependent variables.
The regression coefficient takes into account below mentioned equation:

$$Y = a1*x1 + a2*x2 + a3*x3 + c$$

Where Y is dependent variable (biological activity), a's are regression coefficient of respective x(descriptors, independent variable) and c is regression constant.

QSAR study by Principal Component Analysis (PCA)

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Principal component analysis frame the data on new set of axes. Data is to be taken in order of decreasing variance among the data [64-103].

The implification of PCA analysis is that it account for relationship between the physicochemical parameters (independent variables). It then creates new variables (the principal components) which express various information entailed in the independent variables [104-150].

QSAR study by Principal Component Regression (PCR) Analysis

Principal Component Regression analysis takes into account linear regression to commence a model which employs principal components as independent variables. The difference between MLR and PCR is that MLR takes into account physicochemical properties as independent variables whereas PCR uses principal components generated by PCA as independent variables.

RESULTS And DISCUSSION

MLR analysis

The relationship between the IC_{50} values as various descriptors by MLR was denoted by QSAR equation:

$$Y1 = + 0.1174 (\pm 0.1277) X1 - 1.0848 (\pm 6.3081) X2 - 7.0215 (\pm 4.3482) X3 + 1.9667 (\pm 6.7297) X4 + 12.3227 (\pm 5.5886) X5 + 59.5900 (\pm 24.0864)$$

(n = 50 ; R = 0.722 ; s = 16.945 ; F = 9.587 ; $p < 0.0001$; Q2 = 0.367 ; SPress = 19.489 ; SDEP = 18.468,R^2=0.5214)

This model explains 52.1% of variance in the inhibitory action of quinolones derivate against MCF-7 cell lines. Standard deviation is coming out to be 16.94 which is not good. In addition to it doesn't have good predictive capacity (Q2 = 0.367; SPress = 19.489).Table 2 shows correlation matrix among all the five descriptors and also with biological activity.

Table 2: Correlation matrix.

	Y1	X1	X2	X3	X4	X5
Y1	1.00	0.237	0.204	0.392	0.046	0.482
X1	0.237	1.00	0.735	0.238	0.122	0.567
X2	0.204	0.735	1.000	0.401	0.411	0.196
X3	0.392	0.238	0.401	1.00	0.567	0.132
X4	0.046	0.122	0.411	0.567	1.00	0.650
X5	0.482	0.576	0.196	0.132	0.650	1.00

Where Y1=IC50 value, X1=molecular weight, X2=Hydrogen bond acceptor, X3=Hydrogen bond donor, X4=log P, X5=log S

The above results show that there is not good relationship between biological activity and all the five physicochemical properties because all the values are very less than 1.

A QSAR model when employed only to Molecular weight (X1), shows following statistics:

$$Y1 = - 0.0650 (\pm 0.0777) X1 + 49.9060 (\pm 30.4112)$$

(n = 50 ; R = 0.237 ; s = 22.783 ; F = 2.857 ; p = 0.0975 ; R^2=0.0562; Q2 = Not Pred. ; SPress = Not Pred. ; SDEP = Not Pred.)

This means that molecular weight alone can explain 5.62% variance in biological data. Similarly when QSAR model was employed only to Hydrogen bond acceptor(X2), Hydrogen bond donor(X3), log P(X4), log S(X5) shows alone 4.15%, 15.33%, 0.22%, 23.2% variance in biological data.

CORRELATION ANALYSIS

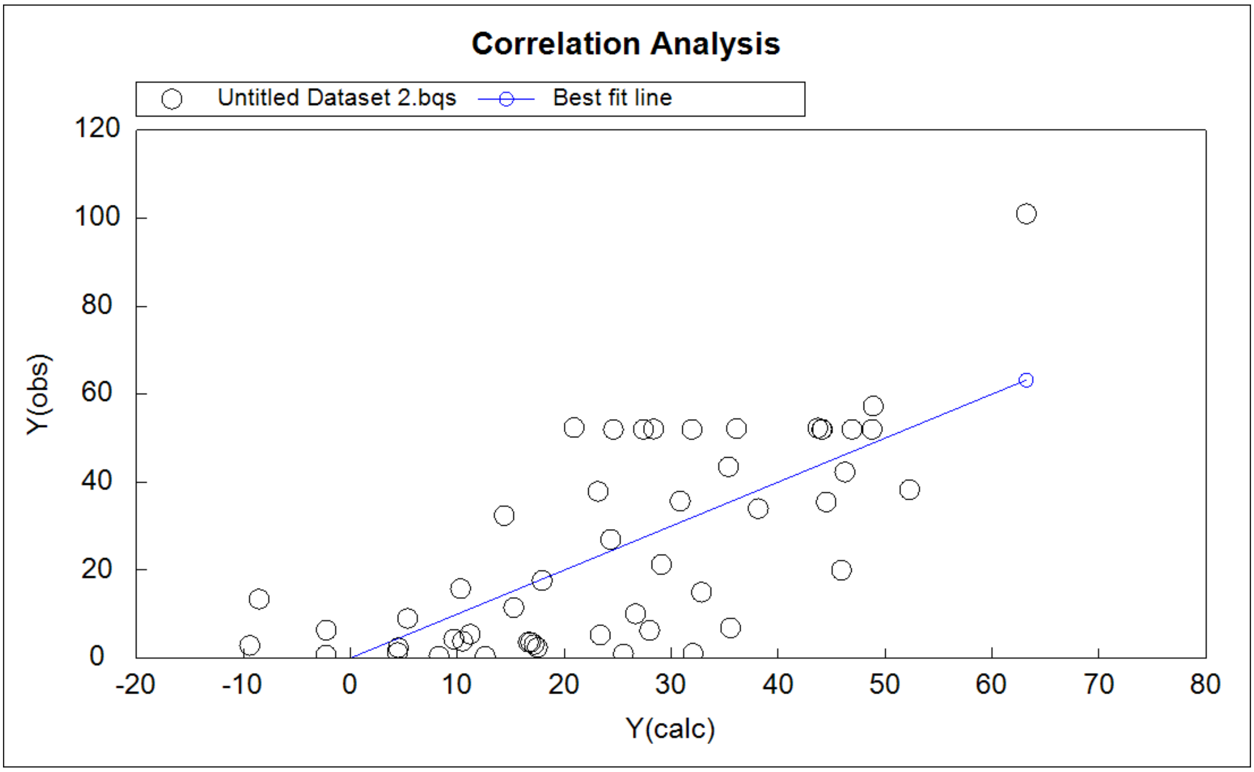

Figure 1. Plot showing correlation between predicted and observed biological activity against MCF-7.

PCA Analysis

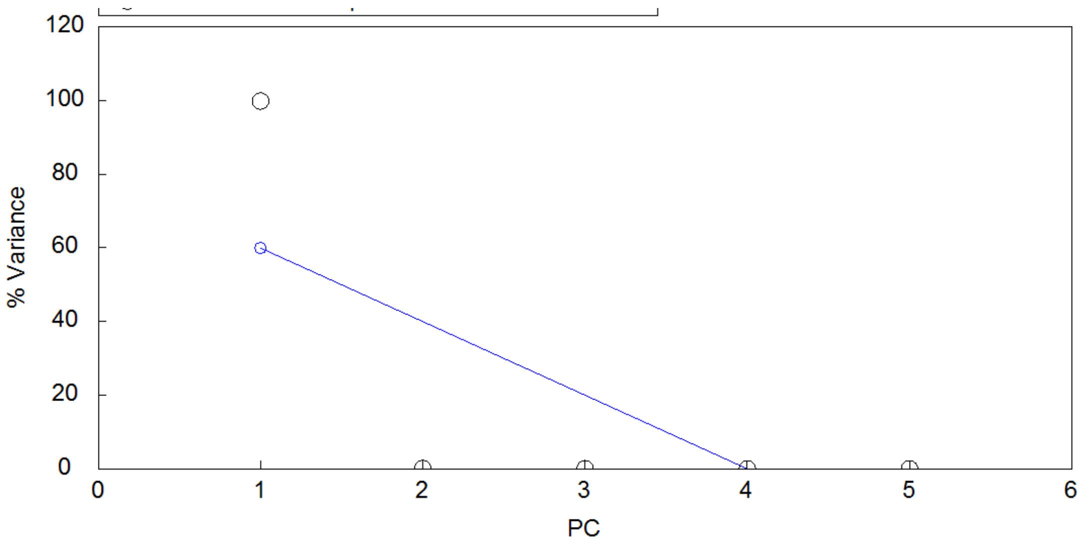

Figure 2. Graph showing % variance among Principal Components.

PCR Analysis

QSAR equation generated is

$$Y1 = -5.1198 (\pm 3.2886) PC1 + 3.7778 (\pm 3.3900) PC2 + 14.9172 (\pm 6.5635) PC3 - 19.8527 (\pm 11.1467) PC4 + 25.0610 (\pm 4.7891)$$

(n = 50; R = 0.722; $R^2 = 0.5214$;s = 16.756 ; F = 12.256 ; $p < 0.0001$; Q2 = 0.410 ; SPress = 18.606 ; SDEP = 17.831)

This model explains 52.1% of variance. Standard deviation is coming out to be 16.75 which is not good. In addition to it doesn't have good predictive capacity (Q2 = 0.410; SPress = 18.606).

CONCLUSION

QSAR results obtained to analyse structural features of all the fifty quinolones derivatives to inhibit MCF-7 cell line provides good information what is required for the molecule. Out of all three MLR is the best model to develop a relationship between the biological activity(IC50) on MCF -7 cell lines against the molecular descriptors of various quinoline derivatives.

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