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Quantitative Structure–activity Relationship Studies of Flavonoids Substituted as Anticancer Agents Activity against the Growth of the Hepatic Cancer Cell lines HepG2

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Abstract

Quantitative Structure–Activity Relationship (QSAR) models, based on molecular descriptors, derived from molecular structures, have been used for the prediction for computed the Hepatic Cancer Cell lines HepG2 of flavonoids substituted. QSAR model including some molecular descriptors, regression quality indicates that these descriptors provide valuable information and have significant role in the assessment of the cytotoxicity of compounds under study. Four QSAR equations, for the prediction of cytotoxicity, have been drawn up by using the multiple regression technique, (Eqs 1-4) with the values of R^2 ranged from 0.767-0.797, Q^2 ranged from 0.765-0.796 and the values of S ranged from 7.051-7.391, while the values of F ranged from 9.328-10.354. The results have shown excellent model by Eq 4. with high R^2,F and minimum S by using eight parameters [Gm, nO, nH, nCIC, nBM, nAB, D.M and Ku], and have found and indicated that these parameters have significant role in determining the properties of cytotoxicity. This result encourages the application of QSAR to a wider selection of compounds properties.

Keywords: *QASR, Flavonoids substituted, Hepatic cancer, HepG2*

1. Introduction

Flavonoids are a large class of natural compounds with a C_6–C_3–C_6 skeleton substituted by various groups. They have been receiving great interests because of a wide spectrum of biological activities exhibited, such as anti-allergic (Ververidis et al., 2007), anti-inflammatory (Spencer, 2008.) antimicrobial (Cushnie&Lamb,2005) & anticancer effects (Lotito & Frei,2006).

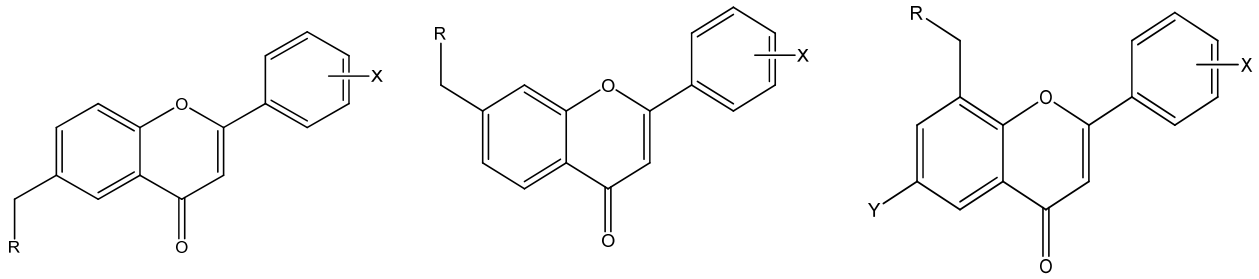
Cancer is one of the most formidable afflictions in the world. Although cancer mortality is the second cause to heart disorders, the first is steadily increasing, while the latter is leveling off. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer causes about 13% of all deaths. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke(Thompson.,1995), radiation(Yang & Korsmeyer.,1996), chemicals(Reed.,1994), or infectious agents (Ambrosini., 1997) & (Clem.,1994).The quantitative structure-activity relationship/the quantitative structure- property relationship (QSAR/QSPR) is a successful strategy for prediction of surfactant properties based on modeling between calculated descriptors from molecular structures of the surfactants and chemical or physical properties of the solution. QSAR has also become a well-established and proven technique to correlate diverse physicochemical properties of compounds, ranging from simple to complex, with molecular structure, through a variety of descriptors of the chemical structures. Most QSAR/QSPR treatments utilize a program to calculate descriptors and then try to select a small number of descriptors in a purely empirical fashion to form an equation. QSAR/QSPR methodology has been aided by new software tools, which allow chemists to elucidate and to understand how molecular structure influences properties (Alan et al, 2006, Ashrafi et al., kawkab et al., 2016., Bahjat et al., 2011., Kawkab et al., 2012., Vladyslav et al., 2004., Aihong et al., 2007, Sadiq et al., 2015). The aim of work is to study QSAR investigation on 30 flavonoids as anticancer agents activity against the growth of the hepatic cancer Cell lines HepG2.

2. Modeling and Geometry Optimization

The quantum chemical calculations were performed for 30 flavonoids derivatives. The final geometries were obtained

with the semi-empirical PM3 method in the Hyperchem program 8.0

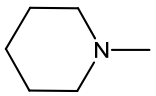
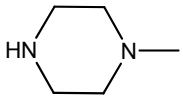
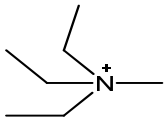
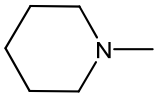
(www.hyper.com). The resulted optimized geometries were subjected to further single point calculations using B3LYP method at the 6-31G(d) basis set using Gaussian program (Frisch et al, 2004, www .gaussian.com) & (Lee, 1998). Some descriptors calculations use Dragon program (Talete, 2015, www.talete.mi.it). The experimental anticancer activity data of 30 compounds under study has been taken from reference (Xiao-Bing et al., 2012). Structures of 30 compounds are shown in Figure 1 and Table1.

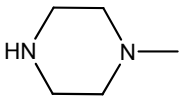
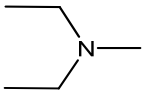
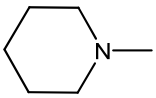
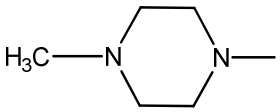
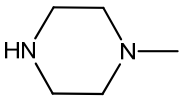
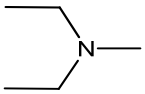
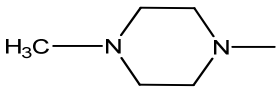
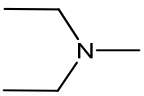
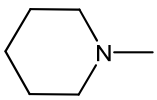
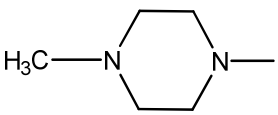
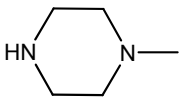
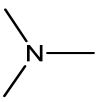
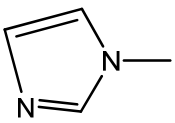
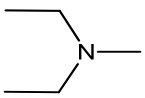
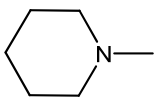


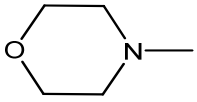
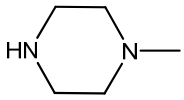
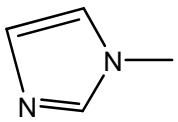
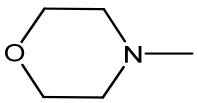
(17) (18) (19)

Figure 1.Molecular structure of the compounds under study.

Table 1. The target compounds in series 17, 18 and 19.

Compound	R	X	Y
17c	**H**	**2-Cl**	**-**
17e	**H**	**4-NH_2**	**-**
17n		**4-Cl**	**-**
17q		**4-Cl**	**-**
17u		**2-Cl**	**-**
17x		**1-3B**	**-**
18b	**H**	**4-Cl**	**-**
18c	**H**	**2-Cl**	**-**
18e	**H**	**2-NH_2**	

18j		**4-NO_2**	**-**
18k		**2-Cl**	**-**
18l		**2-Cl**	**-**
18m		**2-Cl**	**-**
18o		**2-Cl**	**-**
19e	**H**	**4′-NH_2**	**Cl**
19f		**4′-NO2**	**H**
19g		**4′-NO_2**	**H**
19i		**4′-NO_2**	**Cl**
19j		**4′-NO_2**	**Cl**
19k		**4′-NO_2**	**Cl**
19m		**4′-NO_2**	**Cl**
19n		**4′-NO_2**	**Cl**
19o		**4′-NO_2**	**Cl**
19p		**2′-Cl**	**Cl**
19q		**2′-Cl**	**Cl**

19s		**2′-Cl**	**Cl**
19t		**2′-Cl**	**Cl**
19u		**2′-Cl**	**Cl**
19v		**2′-Cl**	**Cl**
19w		**4′-Cl**	**Cl**

3. Materials and Methods

3.1 Quantitative Structure–Activity Relationship (QSAR)

To screen out potential leads against hepatic cancer cell lines HepG2**,** 30 compounds (17c & 19w), as described in Ref (Xiao-Bing et al., 2012) which used in the training set for the development of a robust QSAR model by method Multiple Linear Regression (MLR), demonstrate the usefulness and focus of some of the parameters in deriving predictive QSAR models (Georgi et al., 2014., Zahra et al., 2015, Sanmati & Priyanka., 2011). The relation between the Hepatic cancer cell lines HepG2 and quantum chemical calculated parameters, and identical molecular descriptors to calculate R^2, S and F. Linear regression analyses are performed to find the best correlation between various biological activity indices and the biological activities of the studied**.** A large number of molecular descriptors (22) were calculated which include number of double bond (nAB), dipole moment (μ), Hydration Energy (H.E), number of Hydrogen atoms(nH), number of Oxygen atoms(nO), number of rings (nCIC), number of multiple bonds (nBM), number of un-substituted benzene (nCbH), numbers of atoms (nAT), G total symmetry index/weighted by atomic masses (Gm), K global shape index/un-weighted (Ku), HOMO and LUMO energies, Energy Gap, logP, Polarizability (pol), Mass, Volume and Refractivity (ref). A brief description of the descriptors used in this study is represented in Table2.

Table 2. Descriptors as the Independent Variables Used for QSAR Analysis of Compounds

Comp.	Exp.	nAB	H.E	D.M	nCIC	nBM	nCbH	nAT	Gm	Ku	HOMO	LUMO	E.GAP	log P	nH	nO	pol.	ref.	Mass	Volume
17c	6.23	12	-3.14	4.509	3	14	7	30	0.198	0.762	-6.281	-1.517	4.7633906	0.92	11	2	29.12	84.06	270.72	752.86
17e	21.3	12	-8.89	5.108	3	14	7	32	0.188	0.802	-5.68	-1.475	4.2052807	-0.58	13	2	28.54	82.9	251.28	755.91
17n	14	12	-2.57	3.053	4	14	6	42	0.207	0.821	-5.534	-1.625	3.9086742	0.32	17	2	38.96	110.26	374.27	993.49
17q	2.69	12	-5.45	3.605	4	14	7	44	0.18	0.825	-5.172	-1.909	3.262943	-0.22	19	2	38.39	108.32	354.84	988.6
17u	61	12	-0.91	13.737	3	13	7	50	0.163	0.608	-4.875	-1.736	1.7510665	0.89	25	2	39.26	108.82	358.89	988.01
17x	2.64	12	-7.97	5.218	4	14	7	47	0.166	0.824	-5.387	-1.461	3.9266339	-0.44	22	2	38.29	108.54	334.42	997.09
18b	6.83	12	-3.11	3.663	3	14	7	30	0.217	0.712	-6.342	-1.868	4.4730428	0.92	11	2	29.12	84.06	270.72	762.96
18c	28.3	12	-3.08	5.161	3	14	7	30	0.221	0.696	-6.198	-1.808	4.3897753	0.92	11	2	29.12	84.06	270.72	752.34
18e	40.5	12	-8.74	4.987	3	8	7	32	0.199	0.743	-5.821	-1.588	4.2333086	-0.58	13	2	28.54	82.9	251.28	754.32
18j	4.53	12	-11.4	5.437	4	16	7	46	0.166	0.706	-5.233	-2.985	2.2479503	-0.81	19	4	38.3	109.82	365.39	1006.77
18k	10.7	12	-2.07	3.716	3	14	8	44	0.167	0.767	-6.011	-1.79	4.2207913	1.25	21	2	35.88	102.35	307.39	954.63
18l	3.64	12	-2.15	4.042	4	14	7	45	0.168	0.68	-5.586	-1.908	3.6784641	1.06	20	2	38.87	109.71	353.85	1003.01
18m	14.2	12	-2.46	4.768	4	14	7	47	0.153	0.708	-5.398	-1.536	3.8621424	0.14	21	2	40.22	113.62	368.86	1043.33
18o	2.58	12	-5.23	5.164	4	14	7	44	0.162	0.683	-5.529	-1.527	4.0017379	-0.22	19	2	38.39	108.32	354.84	992.45
19e	11.9	12	-8.51	7.215	3	14	6	32	0.191	0.683	-5.82	-1.65	4.1696335	-0.8	12	2	30.47	87.61	285.73	789.47
19f	28.8	12	-7.29	5.347	3	16	7	46	0.158	0.537	-6.022	-2.765	3.2572285	0.43	20	4	37.72	108.56	352.39	970.94
19g	2.94	12	-7.98	5.33	4	16	7	49	0.156	0.417	-5.161	-2.942	2.2188339	-0.45	21	4	40.14	115.12	379.42	1028.67
19i	1.19	12	-7.08	4.241	3	16	6	46	0.174	0.535	-6.146	-2.858	3.2879776	0.21	19	4	39.65	113.28	386.83	1014.22
19j	8.91	12	-7.52	3.663	4	16	6	47	0.182	0.575	-5.888	-2.911	2.9777654	0.25	19	4	40.71	115.93	398.85	1036.99
19k	1.76	12	-7.19	5.135	4	16	6	49	0.174	0.578	-6.033	-2.265	3.767446	-0.68	20	4	42.06	119.83	413.86	1023.69
19m	0.243	12	-6.35	3.828	4	16	6	46	0.186	0.581	-5.401	-2.748	2.6528589	-1.04	18	4	40.23	114.54	399.83	995
19n	6.19	12	-8.02	2.937	3	16	6	40	0.177	0.598	-6.241	-3.137	3.1037551	-0.48	15	4	35.78	103.78	358.78	913.82
19o	2.94	17	-12.31	4.817	4	21	6	39	0.202	0.564	-6.456	-3.038	3.4180491	-1.36	12	4	37.78	108.71	381.77	971.17
19p	7.94	12	-1.1	6.383	3	14	6	44	0.162	0.442	-5.944	-1.765	4.1788854	0.8	19	2	39.74	111.78	376.28	994.94
19q	10.7	12	-1.51	6.643	4	14	6	45	0.18	0.495	-5.704	-1.837	3.8667684	0.84	19	2	40.8	114.42	388.29	1030.59
19s	6.81	12	-3.57	5.749	4	14	6	43	0.165	0.481	-5.824	-1.796	4.0273168	-0.23	17	3	39.6	111.36	390.27	990.58
19t	18.7	12	-0.33	10.319	4	14	6	44	0.166	0.497	-3.672	-1.143	2.5290461	-0.44	18	2	40.32	113.04	389.28	970.31
19u	1.87	12	-2.09	4.919	3	14	6	38	0.165	0.52	-5.845	-2.231	3.6134284	0.12	15	2	36.07	102.28	348.23	908.19
19v	3.27	17	-5.96	5.571	4	19	6	37	0.188	0.504	-6.471	-2.187	4.2839222	-0.77	12	2	37.87	107.2	371.22	950.49
19w	6.33	12	-4.01	4.608	4	14	7	43	0.188	0.491	-5.869	-1.907	3.9617368	0	18	3	37.67	106.64	355.82	957.7

Definition of Descriptors Used in This Study: E.Gap =Different between HOMO and LUMO is energy gaps in eV,

HOMO=The energy of Highest Occupied Molecular Orbital in eV, LUMO= The energy of Lowest Unoccupied Molecular Orbital in eV, nAB= number of double bond, μ= dipole moment in Debye, H.E = Hydration Energy in Kcal/mol., nH= number of Hydrogen atoms, nO= number of Oxygen atoms, nCIC= number of rings, nBM= number of multiple bonds, nCbH= number of un substituted benzene, nAT= numbers of atoms, pol= Polarizability, ref.= Refractivity, Gm= G total symmetry index/weighted by atomic masses, Ku= K global shape index/un-weighted.

Results and Discussion

The structures of the studied compounds are shown in Figure 1, and Table 1. In this study, the parameters in Table 2 were used. To establish the statistical correlation, the physicochemical parameters were taken as independent variables and anticancer agents activity against the growth of the Hepatic cancer cell lines HepG2, as dependent variable. The best model was selected on the basis of statistical parameters viz observed with high coefficient of multiple (R^2), sequential Fischer test (F) and low standard error of estimate (S). While the varine inflation factor (VIF) quantifies the severity of multicollinearity least squares regression analysis, were employed to judge the validity of regression equation and evaluated the obtained QSAR models (Freitas et al., 2008 & Thomasa et al., 1996). For the development of QSAR equations, multiple linear regression (MLR) was used for building up the QSAR models. The MLR analysis led to the derivation of one model, with five variables. It is described by the following equation:

The eight- parameter correlations of the flavonoids substituted were given in Eq. (1), depicted in Fig2. The Eq 1. of the flavonoids substitute dare best predicated by reliance on only eight parameter gave good model with correlation coefficient R^2 values for this model of 0.797, and generated by multiple linear regression (MLR) method.

MTT/IC_{50}= 266.368 Gm +5.212 nO+1.447nH - 9.902nCIC - 4.272nBM +4.843nAB +3.882D.M+20.995 Ku-70.495 …(1)

Statistical characteristics of the obtained equation

Q^2=0.796 R^2=0.797 S=7.051 F=10.350

The good relationship between the experimental data predicted the anticancer agents activity against the growth of the Hepatic cancer cell lines HepG2. In this model, values of Gm, nO, nH, nAB, D.M and Ku suggest that the activity increases with the rise values of these descriptors while it decreases with increasing values of both nCIC and nBM since they have a negative values in this equation. Figure 2 shows the relationship between the experimental data and calculated MTT/IC_{50}.

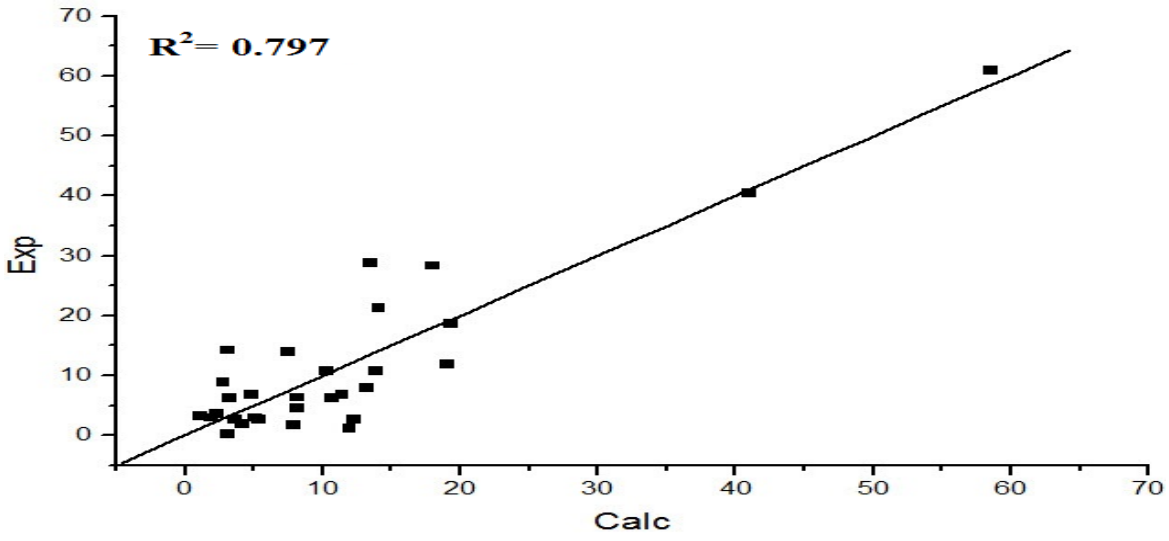


Figure 2. Plot of anticancer agentsactivity against the growth of the hepatic cancer cell lines HepG2prediction versus anticancer agentsactivity against the growth of the hepatic cancer cell lines HepG2experimental usingEq1.

When replacement of a parameters [nH and Ku] in eq 1. by the parameters [nAT and nCbH], gave model predicted in this study Eq 2, the resulting decreasing correlation coefficient, *F*-test statistic and increase standard error means that the mass parameter has weak statistic affect on anticancer agents activity against the growth of the hepatic cancer cell lines HepG2 compared with nAT and nCbH in eq 2.

MTT/IC_{50}= -10.308 nCIC - 4.166 nBM + 4.003nAB+3.832 D.M +0.897 nAT + 322.955Gm+ 5.360 nCbH + 3.649 nO- 100.501 ….(2).

Statistical characteristics of the obtained equation

R^2 =0.794 S=7.113 F=10.124 Q^2=0.793

Figure 3. represents the relationship between the experimental data and predicted anticancer agents activity against the growth of the hepatic cancer cell lines HepG2.

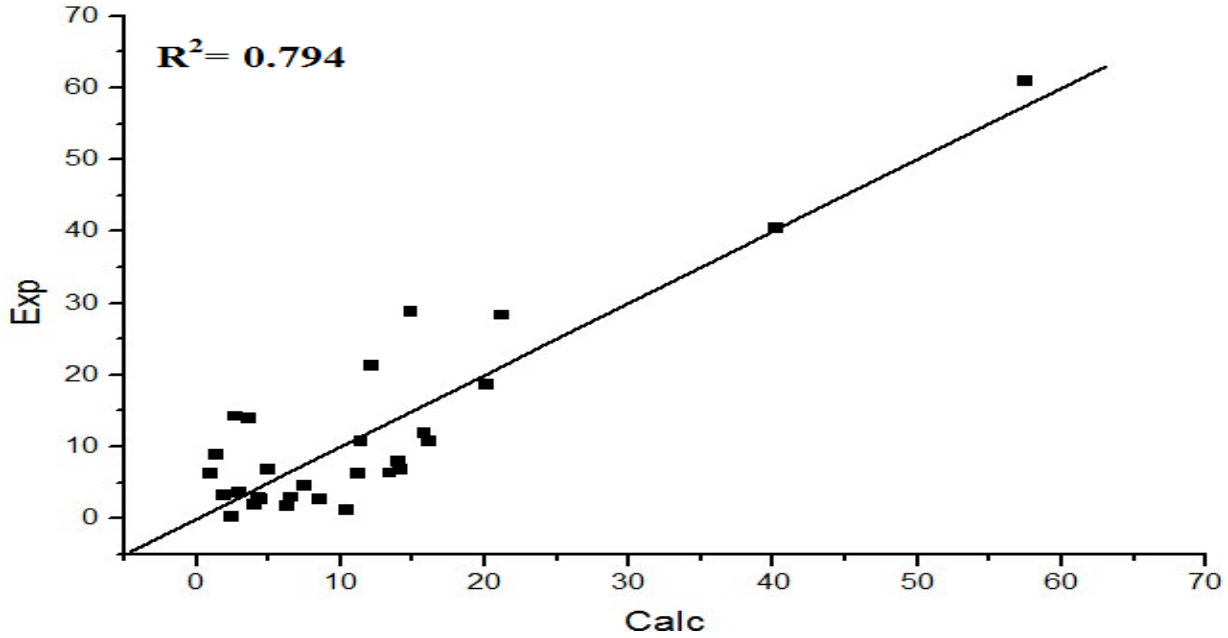


Figure 3. Plot of anticancer agentsactivity against the growth of the hepatic cancer cell lines HepG2 prediction versus anticancer agentsactivity against the growth of the hepatic cancer cell lines HepG2experimental usingEq2.

As well as the good relationship between the experimental data in this model, depending on values of H.E, suggests that the activity increases with rise values of these descriptors. On the other hand, the negative value of H.E suggests the opposite. Figure 4 shows the relationship between the experimental data predicted anticancer agents activity against the growth of the hepatic cancer cell lines HepG2.

MTT/IC_{50} = -11.851 nCIC -3.373 nBM + 3.042nAB+3.686 D.M +1.209 nAT + 364.210Gm+ 4.400 nCbH - 0.544H.E- 101.266 ……(3)

Statistical characteristics of the obtained equation:

R^2 =0.780 S=7.346 F=9.328 Q^2=0.780

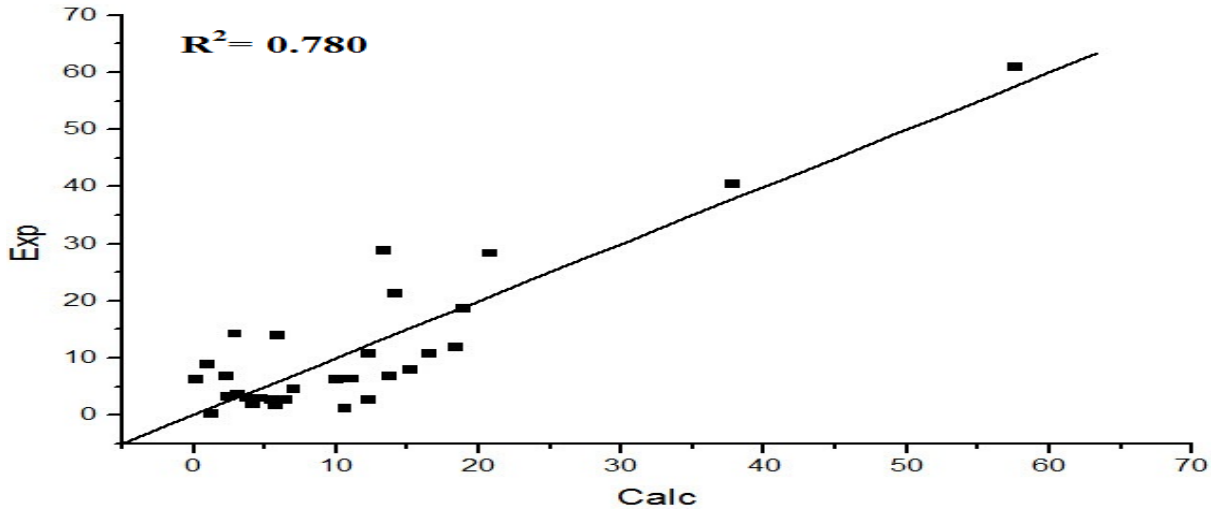


Figure 4. Plot of anticancer agents-activity against the growth of the hepatic cancer cell lines HepG2prediction versus anticancer agents-activity against the growth of the hepatic cancer cell lines HepG2experimental usingEq3.

The seven- parameter correlations of the flavonoids substituted were given in eq. (4), depicted in Figures 5. The Eq. 4 of the anticancer agents activity against the growth of the hepatic cancer cell lines HepG2 flavonoids substituted compounds are good predicted by reliance on only (7) parameters, Good model with $R^2 = 0.767$.

MTT/IC_{50} = -11.901 nCIC -3.112 nBM + 3.214nAB+3.486 D.M +1.186 nAT + 360.171Gm+ 4.580 nCbH +102.601 …….(4)

Statistical characteristics of the obtained equation

R^2 =0.767 S=7.391 F=10.354 Q^2= 0.765

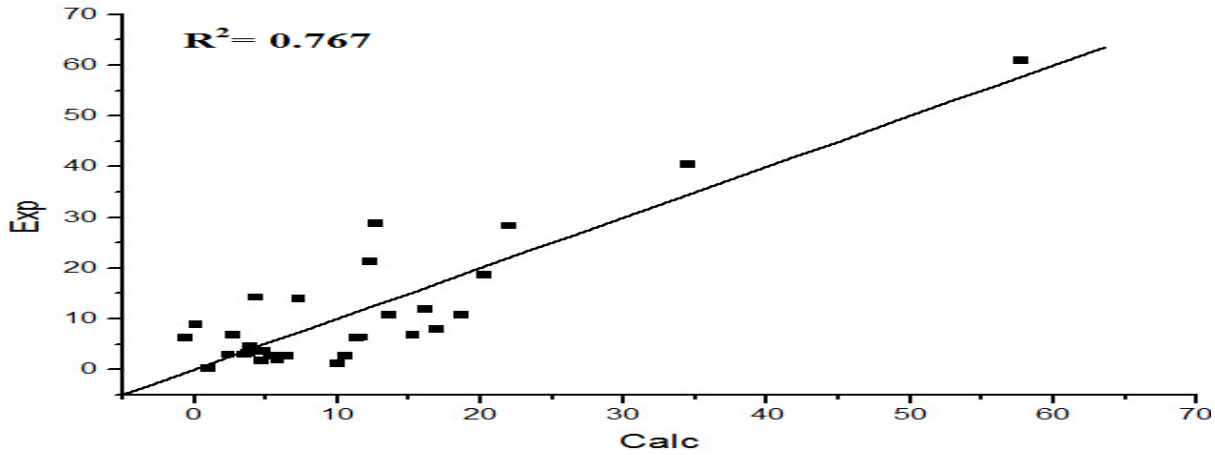


Figure 5. Plot of anticancer agents activity against the growth of the hepatic cancer cell lines HepG2prediction versus anticancer agents activity against the growth of the hepatic cancer cell lines HepG2experimental usingEq3.

The quality of models can be evaluated by correlation coefficient squared (R^2), coefficient of determination, or in the best, by internal validation. Internal model validation was carried out using leave-one-out (LOO-Q^2) method. For calculating q^2, each sample in the training set was eliminated once and the activity of the eliminated sample was predicted by using the model developed by the remaining samples. The Q^2computed using the expression which explains the internal strength of a model. A model is considered acceptable when the value of Q^2 exceeds 0.5. A representative plot showing Q^2 as a function of the correlation coefficient R^2 counts as illustrated in figure 6, for the predicted of anticancer agents-activity against the growth of the hepatic cancer cell lines HepG2data set. (Doreswamy & Chanabasayya., 2013). Obtainedby Eq 1-4.

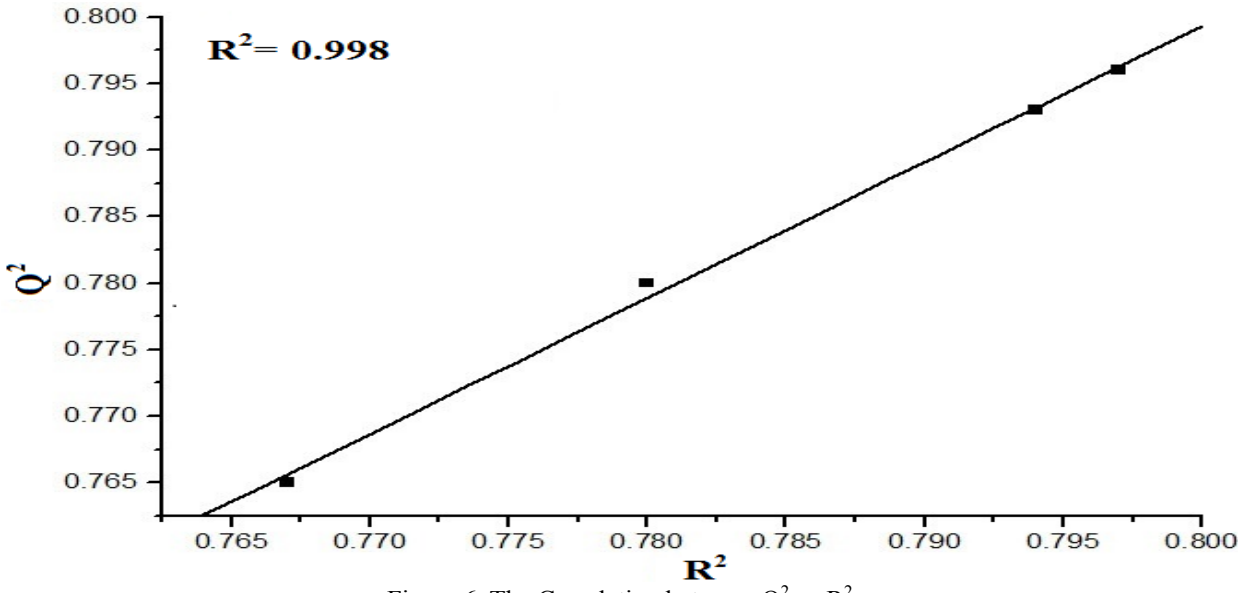


Figure 6. The Correlation between Q^2 vs R^2

Table. 3 shows variance inflation factors of descriptors in eq. 1 ,eq. 2,eq. 3 and eq. 4. The VIF for the descriptors nCIC, nBM, nAB, D.M, nAT, Gm, nCbH, H.E, nO , Ku and nH are fairly large in both equations.

Table 3. The varied inflation factor (VIF) quantifies the severity of multicollinearity least squares regression analysis.

Equations / Descriptor	Eq.4	Eq.3	Eq.2	Eq.1
nCIC	1.941	1.942	2.076	1.527
nBM	2.956	3.084	3.979	3.838
nAB	2.867	2.887	3.076	3.213
D.M	1.360	1.436	1.473	1.675
nAT	4.270	4.279	4.944	-
Gm	2.711	2.714	2.805	3.037
nCbH	1.232	1.237	1.273	-
H.E	-	1.303	-	-
nO	-	-	2.360	2.421
Ku	-	-	-	1.836
nH				3.953

4. Conclusion

Quantum chemical calculated parameters can be successfully used for the derived designer QSAR, capable of predicting the anticancer agents activity against the growth of the hepatic cancer cell lines HepG2 values. The study has indicated that predicted anticancer agents activity against the growth of the hepatic cancer cell lines HepG2 flavonoids substituted can be modeled by multiple linear regression (MLR).The best equation is generated by eight parameters. The model, depending on the eq. 1. (MLR), is the best produced model with good statistical fit as evidentR^2 =0.797, S=7.051 and F=10.350.

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