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Research Article

Quantitative structure activity relationships of cytotoxicity effect on various cancer cells of some imidazo[1,2-α]pyrazine derivatives

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Abstract

We have investigated the quantitative structure activity relationships (QSARs) between quantum chemical parameters and $logIC_{50}^{-1}$ being as values of cytotoxicity effect on various cancer cells of seventeen imidazo[1,2-α]pyrazine derivatives. All of the quantum chemical parameters except for hydrophobic parameter and molar refractivity was calculated by using DFT/B3LYP method and 6-31G (d,p) basis set. The complex, strong, descriptive and interpretable models for QSAR is derived using multiple linear regression analysis as a statistical method. QSAR models show that molecular volume, ionization potential, molecular softness, dipole moment, molar refractivity and hydrophobic parameter are important parameters that can affect the inhibitor activities on cancer cells division of investigated molecules. QSAR models found the regression coefficients for MDAMB-231, MCF-7, Hep G2 and SK-N-SH cells as 1.000, 0.984, 0.926 and 0.997, respectively.

Keywords: Cytotoxicity, Imidazo[1,2-α]pyrazine, inhibition concentration, QSAR, Quantum chemical parameters

1. Introduction

Cancer, after from cardiovascular disease, does incoming order of second in the ratio of dies and the most feared disease. Cancer arise from division of cells in live tissue without permission of autonomic control of body, thus, concept designated by name tumor occurs. The tumors being harmless for body, outspread and located in a specified position in a healthy tissue do not be considered as cancer. Cancer justices to oneself in the way of malignant tumor that penetrate in tissues and organs devastating them (Guyton 1991). To treat this dangerous ailment, surgical intervention, radiotherapy, immunotherapy and the most widely used method chemotherapy are used depending on the kinds of cancer. But, these treatment methods have critical side effects. Therefore, developing new drugs which have anti-cancer activity is very important.

According to literature, investigations on some imidazo[1,2-α]pyrazine derivatives indicate that these molecules have properties such as anti-bacterial (Rival et al. 1992), anti-inflammatory (Abignente et al. 1981), uterine relaxing activity (Vitse et al. 1997a), anti-bronchospastic (Sablayrolles et al. 1984), anti-ulcer (Bonnet et al. 1992), anti-depressant (Lumma et al. 1983), hypoglycemic activity (Meurer et al. 1992), controlling allergic reactions (Brown et al. 2006), useful biological activity on the cardiovascular system (Sablayrolles et al. 1984; Vitse et al. 1999b; Spitzer et al. 1988; Barraclough et al. 1993), particularly anti-cancer activity (Barraclough et al. 1993; Contour-Galcera et al. 2001; Demirayak et al. 2005; Myadaraboina et al. 2010) and potent smooth muscle relaxant activity (Michel et al. 1995). Moreover, these imidazo[1,2-α]pyrazine derivatives have chemiluminescent properties. Example for luciferin, cypridina, renilla, oplophorus and watasenia are one from imidazo[1,2-α]pyrazine derivatives (Toshio et al. 1968; Yoshito et al. 1969; Sumi et al. 1970; Mccapra et al. 1972; Adamczyk et al. 2003; Arrault et al. 2003).

Quantitative structure activity relationship (QSAR) study, which is one of the most important areas in chemometrics, gives useful information in the field of molecular design, mechanism and medicinal chemistry (Schimidi 1997; Hansch et al. 2001; Wold et al. 2001). QSAR models are mathematical equations setting a relationship between chemical structure and biological activity. QSAR models have provided a deeper knowledge about the mechanism of biological activity. Furthermore, QSAR determines the relationship of biologically active molecules with their structural properties. QSAR calculations and quantum chemical parameters provide possibility to compare and discuss of biological activity of a molecule. They also display the biological activity controlled by which structural parameter or parameters. Moreover, QSAR represents one of the most effective computational approaches for inspecting of inhibition mechanism (Winkler 2002; Guha et al. 2004). Typical QSAR study needs to find a set of molecular descriptors with the higher impact on modeling (Gupta et al. 1999; Consonni et al. 2002; Horvarth et al. 2003; Putta et al. 2003). Cytotoxicity effects of the investigated molecules were performed earlier for different cancer lines (Myadaraboina et al. 2010). In the present work, our main subject is to assess QSAR models' reliability for cytotoxicity levels ($logIC_{50}^{-1}$) of some imidazo[1,2-α]pyrazine derivatives. These models were derived using by multiple linear regression analysis. These analyses were designed for $logIC_{50}^{-1}$ as dependent variable and quantum chemical parameters as independent variables.

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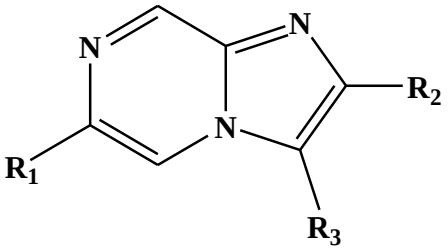
In this present work, QSAR between $logIC_{50}^{-1}$ values and physicochemical parameters of the studied molecules were investigated with MLRA. The effects of the used physicochemical descriptors on the $logIC_{50}^{-1}$ are discussed. In this study, quantum chemical calculations on imidazo[1,2-α]pyrazine derivatives were performed by using DFT-B3LYP/6-31G(d). Afterwards, QSAR between cytotoxicity values ($logIC_{50}^{-1}$) and calculated quantum chemical parameters were done in order to find the predominant parameters affecting the cytotoxicity level.

2. Materials and Methods

2.1. Experimental Data Set

The percentage of cytotoxicity, IC_{50} (Inhibition Concentration), of two human breast cells, MDA-MB-231 (estrogen receptor-negative) and MCF-7 (estrogen receptor-positive), a human neuroblastoma cell line, SK-N-SH, and a human hepatocellular liver carcinoma cells, Hep G2 and synthesis procedure of studied molecules were reported before in literature (Myadaraboina et al. 2010). The $logIC_{50}^{-1}$ values of investigated derivatives is listed in Table 1.

Table 1. Molecular structure and IUPAC name of imidazol[1,2-α]pyrazine derivatives.



No	IUPAC name	R_1	R_2	R_3
1	3-(6-methylimidazo[1,2-a]pyrazin-2-yl)-2H-chromen-2-one	CH_3	3-Coumarinly	H
2	2-tert-butyl-6-methylimidazo[1,2-a]pyrazine	CH_3	t-Butyl	H
3	3-bromo-2-(4-fluorophenyl)-6-methylimidazo[1,2-a]pyrazine	CH_3	4-C_6H_4F	Br
4	3-(3-bromo-6-methylimidazo[1,2-a]pyrazin-2-yl)-2H-chromen-2-one	CH_3	3-Coumarinly	Br
5	2-(4-fluorophenyl)-6-methylimidazo[1,2-a]pyrazine-3-carbonitrile	CH_3	4-C_6H_4F	CN
6	6-methyl-2-phenylimidazo[1,2-a]pyrazine	CH_3	Phenyl	H
7	6-methyl-2-p-tolylimidazo[1,2-a]pyrazine	CH_3	4-$C_6H_4CH_3$	H
8	2-(4-fluorophenyl)-6-methylimidazo[1,2-a]pyrazine	CH_3	4-C_6H_4F	H
9	2-phenylimidazo[1,2-a]pyrazine	H	Phenyl	H
10	2-(4-fluorophenyl)imidazo[1,2-a]pyrazine	H	4-C_6H_4F	H
11	2-p-tolylimidazo[1,2-a]pyrazine	H	4-$C_6H_4CH_3$	H
12	3-bromo-6-methyl-2-phenylimidazo[1,2-a]pyrazine	CH_3	Phenyl	Br
13	3-bromo-6-methyl-2-p-tolylimidazo[1,2-a]pyrazine	CH_3	4-$C_6H_4CH_3$	Br
14	3-bromo-2-tert-butyl-6-methylimidazo[1,2-a]pyrazine	CH_3	t-Butyl	Br
15	3-bromo-2-phenylimidazo[1,2-a]pyrazine	H	Phenyl	H
16	3-bromo-2-(4-fluorophenyl)imidazo[1,2-a]pyrazine	H	4-C_6H_4F	Br
17	3-bromo-2-tert-butylimidazo[1,2-a]pyrazine	H	t-Butyl	Br

2.2. QSAR Data Set

In the results of quantum chemical calculations, physicochemical descriptors; the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), band gap energy (E_{LUMO}-E_{HOMO} = ΔE), electrophilic index (ω), molecular hardness (η), molecular softness (S), chemical potential (CP), dipole moment (μ), molecular polarizability (<α>), electronegativity (χ), ionization potential (IP), electron affinity (EA), molecular volume (V_m), octanol–water partition coefficient (hydrophobic parameter (log *P*)), molar refractivity (MR) were determined (Sıdır et al. 2011).

2.3 Calculation Methodology

2.3.1 Quantum Chemical Calculation

All of the molecular structures were constructed by using ChemDraw Ultra 8.0. For every molecule, structure was suitably changed considering its structural features copied to Chem3D Ultra 8.0 to create 3-D model ,the model was subjected to energy minimization using (Dewar et al. 1985). The lowest energy structure was used for each molecule to calculate water-octanol partition coefficient (log *P*) and molar refractivity (MR). Octanol-water partition coefficient and molar refractivity of investigated molecules were calculated by ChemOffice 2004 software. Structures of entire molecules were submitted to HF/3-21G level of theory for geometry conformational search. Conformational analysis of these molecules was performed by Gaussian 09W program. Only those conformations, which are the most stable for a given compound, have been used. The other calculations were carried out by Gaussian09W software (Frisch et al. 2009).

The molecular structure of seventeen imidazo[1,2-α]pyrazine derivatives in the ground state are optimized by using B3LYP method with the standart 6-31G(d,p) basis set. Moreover, the frequency calculations were performed to verify the optimized structures to be at an energy minimum. The quantum chemical parameters of the whole molecules were calculated by using Gaussian09W for quantitative structure activity relationship of the investigated molecules.

Table 2. The observed $logIC_{50}^{-1}$, predicted $logIC_{50}^{-1}$ and residual values between observed $logIC_{50}^{-1}$ and predicted $logIC_{50}^{-1}$ of imidazol [1,2-α] pyrazine derivatives.

Cytotoxicity	Observed $logIC_{50}^{-1}$[a]				Predicted $logIC_{50}^{-1}$[b]				Residual			
value	MDAMB-213	SK-N-SH	HepG-2	MCF-7	MDAMB-231	SK-N-SH	HepG-2	MCF-7	MDAMB-231	SK-N-SH	HepG-2	MCF-7
1	-	-	-2.009	-	-	-	-2.167	-	-	-	0.158	-
2	-	-1.981	-2.997	-	-	-2.226	-2.943	-	-	0.245	-0.054	-
3	-2.283	-1.140	-2.789	-1.111	-2.127	-1.346	-2.786	-1.171	-0.16	0.206	-0.003	0.060
4	-	-2.007	-2.954	-2.863	-	-2.207	-3.162	-2.896	-	0.2	0.208	0.033
5	-2.064	-2.016	-1.998	-1.890	-1.908	-2.169	-2.203	-1.912	-0.16	0.153	0.205	0.022
6	-	-0.982	-	-	-	-1.903	-	-	-	0.921	-	-
7	-	-1.033	-	-	-	-1.213	-1.561	-2.415	-	0.18	-	-
8	-2.017	-2.202	-2.028	-1.984	-1.868	-1.126	-2.179	-2.016	-0.15	-1.076	0.151	0.032
9	-	-	-	-2.982	-	-	-	-2.933	-	-	-	-0.049
10	-2.133	-2.072	-2.867	-2.149	-2.003	-2.277	-3.019	-2.223	-0.13	0.205	0.152	0.074
11	-	-	-2.017	-	-	-	-2.273	-	-	-	0.256	-
12	-1.182	0.000	-1.786	-0.792	-2.176	-1.847	-1.956	-2.170	0.99	1.847	0.17	1.378
13	-2.228	-0.978	-1.930	-1.396	-2.052	-1.017	-2.041	-1.474	-0.18	0.039	0.111	0.078
14	-2.234	-2.091	-2.090	-2.033	-2.096	-2.217	-2.461	-1.915	-0.14	0.126	0.371	-0.118
15	-2.154	-1.960	-2.036	-2.744	-2.013	-2.147	-1.961	-2.765	-0.14	0.187	-0.075	0.021
16	-2.006	-1.906	-1.943	-1.909	-1.855	-2.104	-2.035	-1.860	-0.15	0.198	0.092	-0.049
17	-2.046	-2.057	-2.279	-2.451	-1.921	-2.167	-2.420	-2.613	-0.13	0.11	0.141	0.162

[a] IC_{50} values of investigated molecules were taken reference (Myadarabonia et al. 2010), [b] The $logIC_{50}^{-1}$ values of MDAMB-231, SK-N-SH, Hep-G2 and MCF-7 are used by Eq.(1), Eq.(8), Eq.(6) and Eq.(4), respectively.

2.3.2 Statistical Analysis

In this study, multiple linear regression method was used to investigate quantitative structure-activity relationship between $logIC_{50}^{-1}$ values and physicochemical parameters. This statistical method has been applied by using the statistical software SPSS 15.0 and Origin Pro7.5 package programs. In here, these statistical methods are taking physicochemical parameters as independent variable and $logIC_{50}^{-1}$ as a dependent variable. The whole posterior probabilities used for calculated descriptors have been considered for QSAR statistical calculation. The models were generated by using the MLRA. The derived models were assessed with correlation coefficient, high regression coefficient, low standard deviation, high ability for prediction and high F statistic value.

3. Results and Discussion

Molecular structure and IUPAC names of imidazo[1,2-α]pyrazine derivatives are depicted in the Table 1. The observed $logIC_{50}^{-1}$, predicted $logIC_{50}^{-1}$ and residual values between observed $logIC_{50}^{-1}$ and predicted $logIC_{50}^{-1}$ of imidazol [1,2-α] pyrazine derivatives are listed in Table 2. Physicochemical parameters have been used to research QSAR between $logIC_{50}^{-1}$ and theoretically calculated parameters. The independent variables used for MLRA are listed in Table 3. The ideal method derived with MLRA is one that has high correlation coefficient (R), high regression coefficient (R^2), low standard deviation, low standard error (SE), high ability for prediction and high F statistic value. F statistic shows the mean squares between treatments to the residuals. All of the models derived for each independent variable has standard deviation. The QSAR models for MDAMB–231, MCF–7, Hep G2 and SK-N-SH are as following, respectively.

Considering the best correlation coefficients and sigma values obtained by excluding molecule 12, three QSAR models have been derived for experimentally determined cytotoxicity of MDAMB-231 cell lines. When eight molecules have been taken into account, the best model we have obtained is Eq.(1) which is eight parametric regression equation. This model has good statistical characteristic as evident from its R^2 = 1 and P = 0.000 values. In addition, Eq.(2) has a satisfactory predictive power as evident from its R^2=0.998, R=0.999, F=88.487, P=0.082 and SE=0.0116. In the case of N=9, the second model is Eq.(2) which is a seven parametric regression equation. Even though statistical characteristics of Eq.(2) have good statistical fit and satisfactory, it is slightly lower in comparison with those of Eq.(1). Only one difference between Eq.(1) and Eq.(2) is removal of $(\log P)^2$. When log *P* parameter were treated as outlier, the best model obtained is Eq.(3) which is a seven parametric regression equation with very good statistical fit. The Eq.(3) has a few statistical properties such as R^2=0.992, R=0.996, F=17.599, P=0.182 and SE=0.02596. According to Eq.(1), $logIC_{50}^{-1}$ is precisely characterized by the molecular volume, ionization potential, molecular hardness, dipole moment, hydrophobic parameter and polarizability. The biggest contribution to $logIC_{50}^{-1}$ is provided by molecular hardness with the coefficient of

+2.265. As can be seen from the three models given below, cytotoxicity depends on the molecular volume, ionization potential, molecular hardness, dipole moment, hydrophobic parameter, molar refractivity and polarizability. The QSAR models are follows.

QSAR models for MDAMB–231;

$\log IC_{50}^{-1}$ =-14.406+0.009V_m+0.209IP+2.265η+0.293μ-0.682log *P*+0.192MR-0.039α-0.030(log *P*)^2 (1)
R^2=1; R=1; n=9; P=0.000

Molecule: 3, 5, 8, 10, 13, 14, 15, 16, 17

$\log IC_{50}^{-1}$ =-16.457(±1.827)+0.009(±0.001)V_m+0.260 (±0.042)IP+2.642(±0.441)η+0.353(±0.046)μ+0.229(±0.030) MR-0.047(±0.006)α-0.964(±0.114)log *P* (2)
R^2=0.998; R=0.999; F=88.487; n=9; P=0.082; SE=0.0116

Molecule: 3, 5, 8, 10, 13, 14, 15, 16, 17

$\log IC_{50}^{-1}$ =-8.673(±2.196)+0.007(±0.001)V_m+0.113(±0.113)IP+1.137(±0.640)η+0.132(±0.054)μ+0.089(±0.033)MR-0.020 (±0.007)α-0.093(±0.025) (log *P*)^2 (3)
R^2=0.992; R=0.996; F=17.599; n=9; P=0.182; SE=0.02596

Molecule: 3, 5, 8, 10, 13, 14, 15, 16, 17

Increasing in molecular hardness gives rise to decrease in $\log IC_{50}^{-1}$. $\log IC_{50}^{-1}$ has a negative correlation with log *P* and (log *P*)^2. Thus, it is also observed that cytotoxicity increases while increasing of log *P* value[38]. In addition, $\log IC_{50}^{-1}$ is directly proportional with molecular volume and molar refractivity.

The two QSAR models for cytotoxicity were obtained with good correlation coefficient (R^2) and sigma values (P) for MCF-7 cancer cells line. Eq.(4), including eleven molecules, gives good statistical characteristics. In that case, the model has R^2=0.984, R=0.992, F=6.673, P=0.292 and SE=0.2380. If hydrophobic parameter and polarizability are not included in the MLRA calculation, its statistical parameters are found as R^2=0.981, R=0.990, F=22.144, P=0.014 and SE=0.14796. In this case, Eq.(5) is statistically very significant. These models indicate that $\log IC_{50}^{-1}$ has complex mechanism and depends on various physicochemical parameters. Cytotoxicity is mainly contributed by molecular softness and electron affinity among of these physicochemical parameters.

QSAR models for MCF–7;

$\log IC_{50}^{-1}$ =-12.427(±104.241)-0.002(±0.013)V_m+0.184 (±11.924)IP+2.310(±12.169)EA+49.565(±146.171)S+0.008 (±0.879)μ+0.819(±2.965)log *P*-0.447(±0.564)MR+ 0.040(±0.121)α+0.506(±0.376)(log *P*)^2 (4)
R^2=0.984; R=0.992; F=6.673; n=11; P=0.292; SE=0.2380

Molecule: 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 17

$\log IC_{50}^{-1}$ =18.105(±39.917)-3.380(±4.463)IP+6.078 (±4.146)EA+5.994(±50.536)S+0.270(±0.148)μ+0.058(±0.866)log *P*-0.263(±0.067)MR+0.560(±0.196)(log *P*)^2 (5)
R^2=0.981; R=0.990; F=22.144; n=11; P=0.014; SE=0.14796

Molecule: 3, 4, 5, 8, 9, 10, 13, 14, 15, 16, 17

In the QSAR models, P≤0,005 value obtained using the F statistics is meaningful, so QSAR model Eq.(5) including eleven molecules is statistically very significant. As can be seen from Eq.(4), increasing in molecular volume gives rise to increasing in cytotoxicity.

QSAR models (Eq. (6) and (7)) derived for cytotoxicity of Hep G2 cells lines have the best quality statistical values with the regression coefficients (R^2), sigma (P), Fisher (F) value and standard error (SE). Similarly, the other QSAR models, Eq. (6) and (7) depends a lot of molecular descriptor. Model 6 and 7 is nine parametric regression equations of cytotoxicity of inhibition concentration for Hep G2 cells depends on molecular volume, ionization potentials, molecular hardness, molecular softness, dipole moment, hydrophobic parameter, molar refractivity and polarizability. Molecule 12 and molecular hardness descriptor does not considered in these models while below QSAR models are derived by multiple linear regression analysis. If ΔE is considered, R^2 has statistically significant value of 0.919.

QSAR models for Hep G2;

$\log IC_{50}^{-1}$=171.326(±36.521)+0.010(±0.007)V_m-2.159 (±0.663)IP-35.498(±7.442)η-197.342(±48.190)S-0.708 (±0.165)μ+4.621(±1.976)log *P*-0.048(±0.159) MR+0.033 (±0.033)α-1.015(±0.307)(log *P*)^2 (6)
R^2=0.926; R=0.965; F=5.582; n=14; P=0.057; SE=0.21173

Molecule: 1,2, 3, 4, 5, 8,10, 11, 12, 13, 14, 15, 16, 17

$\log IC_{50}^{-1}$ =168.721(±43.963)-17.510(±4.433) ΔE+0.011 (±0.009)V_m-2.107(±0.801)IP-194.562(±57.026)S-0.689 (±0.215)μ+4.464(±2.405)log *P*-0.040(±0.187) MR+0.031 (±0.041)α-0.989(±0.376)(log *P*)^2 (7)
R^2=0.919; R=0.959; F=3.790; n=13; P=0.150; SE=0.24258

Molecule: 1, 2, 3, 4, 5, 8,10, 11, 13, 14, 15, 16, 17

As seen in Eq.(6) and (7), the most contribution to cytotoxicity is from the molecular hardness, while the least one is provided by the polarizability. Increasing in log *P* gives rise to decreasing in $\log IC_{50}^{-1}$ value and increase of (log *P*)^2 increases the $\log IC_{50}^{-1}$ value.

The Eq.(8) and (9) describe the QSAR models for $\log IC_{50}^{-1}$ on SK-N-SH cells of imidazo [1,2-α]pyrazine derivatives. Eq.(8) has good statistical characteristics as evident from its R^2=0.997, R=0.999, F=35.712, P=0.130 and SE=0.0850. Ten physicochemical parameters are used in multiple linear regression equations of this model. The second best model is Eq. 9, which has the eight parametric regression equation. Statistical characteristics of Eq.(9) are slightly lower in comparison with those of Eq.(8), but it has also good statistical properties such as R^2=0.950, R=0.974, F=10.758, P=0.018 and SE=0.25560. In the Eq.(9), molecular volume was omitted. According to below QSAR models, $\log IC_{50}^{-1}$ value is altered by diversity of molecular characteristics. Cytotoxicity is directly proportional to molecular softness of investigated molecules. Besides, molecular volume provides mainly great contribution to cytotoxicity.

QSAR models for SK-N-SH;

$\log IC_{50}^{-1}$ =101.868(±69.555)+0.030(±0.007)V_m-8.803(±8.502)IP+36.106(±4.834)EA223.858(±82.726)S+2.399(±0.447)μ-6.350(±1.790)log *P*+1.282(±0.275)MR-0.211 (±0.056)α-15.773(±5.244)Ω+0.343(±0.194) (log *P*)^2 (8)
R^2=0.997; R=0.999; F=35.712; n=12; P=0.130; SE=0.0850

Molecule: 2, 3, 4, 5, 6, 7, 10, 13, 14, 15, 16, 17

$\log IC_{50}^{-1}$ =-27.135(±186.665)+5.077(±23.458)IP+19.288 (±5.235)EA7.871(±192.502)S+0.699(±0.519)μ+0.102(±2.619)log *P*+0.220(±0.293)MR+0.002(±0.064)α-14.597 (±15.728)Ω-0.190(±0.433) (log *P*)^2 (9)

R^2=0.950; R=0.974; F=10.758; n=12; P=0.018; SE=0.25560

Molecule: 2, 3, 4, 5, 6, 7, 10, 13, 14, 15, 16, 17,

Using the percentage of IC_{50}, which is experimentally determined on four cancer cell lines, we have researched both cytotoxicity that is altered depending on which quantum chemical parameters and how its dependency is. According to derived QSAR models, cytotoxicity for MDAMB-231 cancer cells are mainly governed by molecular hardness, hydrophobic parameter and dipole moment magnitude, while cytotoxicity for MDAMB-231 cancer cells depend on molecular hardness, electron affinity and hydrophobic parameter, respectively. Furthermore, cytotoxicity of Hep G2 cancer cells is changed with molecular softness, molecular hardness and hydrophobic parameter. For SK-N-SH cancer cells, cytotoxicity is exchanged with molecular softness, electron affinity, electrophilic index and hydrophobic parameter magnitudes.

Figure 1 shows the plot of experimental $logIC_{50}^{-1}$ values against the calculated values, which is estimated by using of MLRA equations of Eq(1), (4), (6) and (8) for MDAMB-231, MCF-7, Hep G2 and SK-N-SH, respectively. They indicate that predicted values of $logIC_{50}^{-1}$ are in agreement with the experimental values of $logIC_{50}^{-1}$.

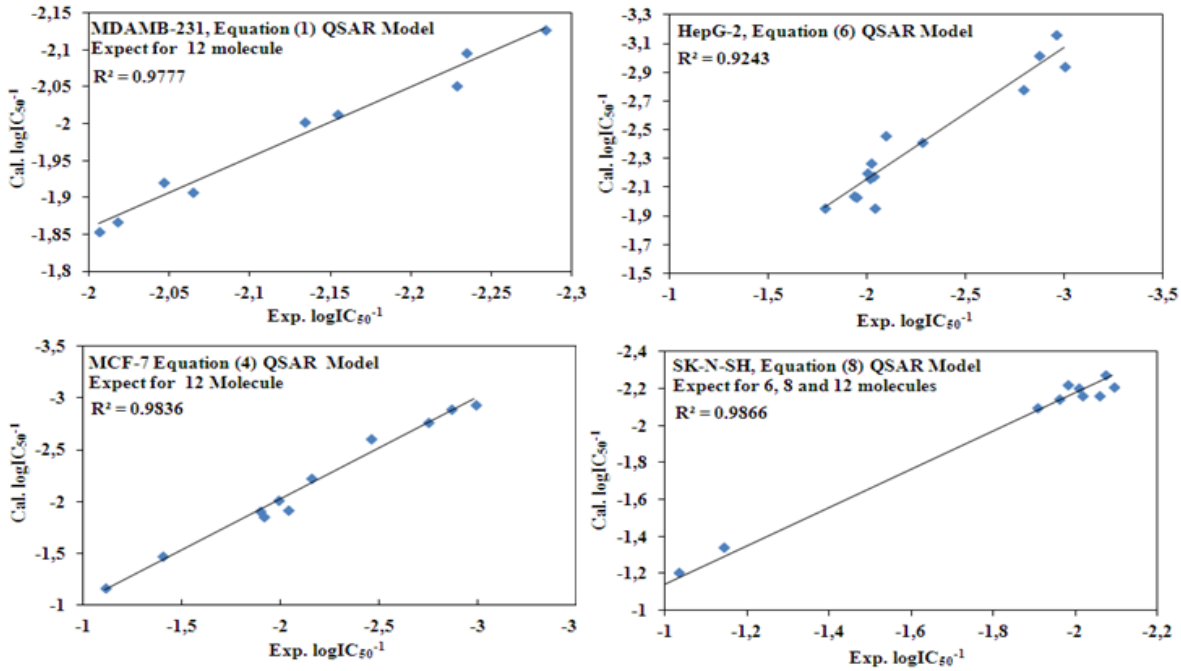


Figure 1. Plots of experimental -$logIC_{50}$ vs. calculated -$logIC_{50}$ of imidazo[1,2-α]pyrazine molecules.

4. Conclusion

A set of quantum chemical parameters is calculated to build a QSAR model that is able to $logIC_{50}^{-1}$ of seventeen imidazo[1,2-α]pyrazine derivatives. Consequently, the molecular descriptors of these molecules are key factors in influencing the value of $logIC_{50}^{-1}$. The physicohemical descriptors are the most important descriptors for the construction of QSAR models. These studies give an insight into electronic properties, like molecular softness and molecular hardness, play the dominant role in modulating the cytotoxicity values. Moreover, cytotoxicity is mainly contributed by hydrophobic parameter.

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