Quantitative Structure–Activity Relationships of Selective Antagonists of Glucagon Receptor Using QuaSAR Descriptors

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In the present paper, quantitative structure activity relationship (QSAR) approach was applied to understand the affinity and selectivity of a novel series of triaryl imidazole derivatives towards glucagon receptor. Statistically significant and highly predictive QSARs were derived for glucagon receptor inhibition by triaryl imidazoles using QuaSAR descriptors of molecular operating environment (MOE) employing computer-assisted multiple regression procedure. The generated QSAR models revealed that factors related to hydrophobicity, molecular shape and geometry predominantly influences glucagon receptor binding affinity of the triaryl imidazoles indicating the relevance of shape specific steric interactions between the molecule and the receptor. Further, QSAR models formulated for selective inhibition of glucagon receptor over p38 mitogen activated protein (MAP) kinase of the compounds in the series highlights that the same structural features, which influence the glucagon receptor affinity, also contribute to their selective inhibition.

Key words diabetes; triaryl imidazole; quantitative structure activity relationship (QSAR); molecular operating environment (MOE)

Diabetes is the root cause of several chronic and progressive diseases, which has direct relationship with complications such as neuropathy, nephropathy, retinopathy, atherosclerosis and coronary artery disease.[1] More than 90% of diabetic patients suffer from type 2 diabetes (NIDDM), which is characterized by insulin resistance and hyperglycemia.[2] The search for effective therapies is earnest along several mechanistic strategies.[3] The search found that Glucagon a 29-aminoacid peptide produced in the α-cells of the pancreas is a major counter regulatory hormone to insulin, stimulating glycogenolysis and gluconeogenesis.[4] Binding of glucagons to its receptor, which signals *via*-G-proteins stimulates adenylcyclase and increases free Ca^{2+} resulting in increased glucose output. The bihormonal hypothesis proposed that glucagon contribute to elevated levels of glucose in diabetics.[5]

A strong body of evidence has prompted the pursuit of glucagons receptor antagonist for the treatment of type II diabetes lowers fasting plasma glucose levels and improves glucose tolerance in diabetics. Several peptidyl antagonists of glucagon receptor are known. However the clinical utility of peptidyl antagonists is seriously limited by facile metabolic cleavage. Efforts directed to circumvent this problem led to the development of non-peptide antagonist such as diaminostyryl-dichloroquinoxaline, substituted benzimidazoles, pyridylphenyls and biphenyl derivatives. In further development of this class of potent antidiabetics, Chang *et al.*[6] synthesized and studied structure activity relationships of triaryl imidazole derivatives for human glucagon receptor antagonistic activity and p38 mitogen activated protein kinase (MAP Kinase) inhibitory activity. Although, Chang *et al.* pointed out certain structural features important for inhibition of the glucagon receptor on the basis of structure activity relationship (SAR) studies, information derived from SAR is qualitative and can be fortuitous. Therefore, a quantitative structure activity relationship (QSAR) study was proposed for the abovementioned series of compounds to rationalize structural requirements for increasing binding affinity of triaryl imidazole derivatives to glucagons receptor. A QSAR study sought to explain and predict activities of series of congeners by utilizing empirical descriptors. Further, QSAR enables the investigators to establish *in silico* quantitative models to predict the activity of novel molecules prior to their synthesis and simultaneously provide deeper insight into the mechanism of drug–receptor interaction.

A dataset of 30 compounds out of 41 compounds reported by Chang *et al.*[6] was adopted for the present study after excluding 11 molecules without a well defined biological activity. The experimentally obtained Glucagon receptor antagonistic activity values (IC_{50}) in micromolar units of 30 congeneric triaryl imidazoles were transformed into molar units and subsequently converted to negative logarithmic values prior to the statistical analysis. Table 1 lists the compounds used for the study along with its activity parameter values.

The computing tools used for the present study were molecular operating environment[7] (MOE 2002.03), statistical software SYSTAT[8] (Version 10.2) and inhouse validation program VALSTAT.[9] All the computations were carried out on Compaq PIV workstation. Structures of triaryl imidazole derivatives were sketched by using builder module of MOE software and sketched structures were subsequently energy minimized up to root mean square gradient of 0.01 kcal/mol Å using MMFF94[10] force field. Conformational search of each energy-minimized structure was performed employing stochastic search routine. All the conformers generated for each structure were carefully scrutinized in conformational geometry panel and only the lowest energy conformer of each structure was stored in MOE database for descriptor calculation.

Molecular descriptors were calculated for the lowest energy conformers of the compounds in the series using the QuaSAR module of the molecular modeling software MOE.[11]

Over 180 descriptors programmed into MOE were calcu-

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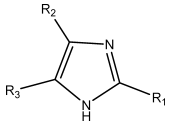
Table 1. Structure of the Compounds Selected for QSAR Study



S. No	R_1	R_2	R_3	hGLUR IC_{50} (–Mg, μM)	p38 IC_{50} (μM)
1	(4-Br)Ph	(4-F)Ph	4-Pyridyl	0.27	0.16
2	(3-Br)Ph	(4-F)Ph	4-Pyridyl	1.4	0.15
3	(4-Cl)Ph	(4-F)Ph	4-Pyridyl	0.4	0.08
4	(4-F)Ph	(4-F)Ph	4-Pyridyl	2	0.1
5	(4-I)Ph	(4-F)Ph	4-Pyridyl	0.51	0.1
6	(4-Me)Ph	(4-F)Ph	4-Pyridyl	1.3	0.09
7	(4-*i*Pr)Ph	(4-F)Ph	4-Pyridyl	0.7	0.28
8	(4-Ph)Ph	(4-F)Ph	4-Pyridyl	10	0.3
9	(4-NH_2)Ph	(4-F)Ph	4-Pyridyl	2	0.07
10	(4-OMe)Ph	(4-F)Ph	4-Pyridyl	13	0.1
11	(4-CN)Ph	(4-F)Ph	4-Pyridyl	8	0.21
12	(4-COOMe)Ph	(4-F)Ph	4-Pyridyl	8.7	0.3
13	(5-Br)-2-thienyl	(4-F)Ph	4-Pyridyl	2.2	0.11
14	(4-Br)-2-thienyl	(4-F)Ph	4-Pyridyl	2.8	0.1
15	α-Napthyl	(4-F)Ph	4-Pyridyl	1.5	0.34
16	(4-SMe)Ph	(4-F)Ph	4-Pyridyl	0.49	0.12
17	(4-Br)Ph	Ph	4-Pyridyl	0.782	0.04
18	(4-Cl)Ph	(4-F)Ph	3-Me(4-pyridyl)	1.1	0.02
19	(4-Cl)Ph	(4-Cl)Ph	4-Pyridyl	0.19	0.023
20	(4-Cl)Ph	(4-I)Ph	4-Pyridyl	0.13	0.14
21	(4-Cl)Ph	(4-Ph)Ph	4-Pyridyl	0.14	3.3
22	(4-Cl)Ph	(4-*t*-Bu)Ph	4-Pyridyl	0.13	NA
23	(4-Cl)Ph	(4-*n*-Bu)Ph	4-Pyridyl	0.074	NA
24	(4-Cl)Ph	(3-Ph)Ph	4-Pyridyl	0.061	0.59
25	(4-Cl)Ph	(2-OPh)Ph	4-Pyridyl	0.0065	0.15
26	(4-Cl)Ph	(3-OPh)Ph	4-Pyridyl	0.013	0.22
27	(4-Cl)Ph	(4-OPh)Ph	4-Pyridyl	0.027	0.25
28	(4-Cl)Ph	(2-*O*-*n*-Bu)Ph	4-Pyridyl	0.0085	NA
29	(4-Cl)Ph	(2,4-(*O*-*n*-Pr)$_2$)Ph	4-Pyridyl	0.013	2.4
30	(4-Cl)Ph	(2,4-(*O*-*n*-Bu)$_2$)Ph	4-Pyridyl	0.0065	NA

lated for each molecule in the series. The calculated descriptors were initially screened for invariant nature, insignificance using QuaSAR Contingency module of MOE. QuaSAR-Contingency is a statistical application designed to assist in the selection of descriptors for QSAR. Further, interrelation study was also performed to limit the number of descriptors considered for the study. A final set of 72 molecular descriptors identified by the aforementioned screening procedures was used in the formulation of QSARs (Table 2).

QSAR models were constructed using the reduced descriptor pool as independent variable and the glucagon antagonistic activity parameters as dependent variable by forward stepwise regression analysis employing statistical program SYSTAT 10.2 version.[8] The generated regressions were then refined by a standard regression method with due consideration to the significance of the individual descriptors, the intercorrelation between them and the number of data points. The relationships derived were tested according to the requirements of a meaningful correlation analysis and QSARs were considered only if the multiple correlation coefficient R is above 0.80 or higher variance (R^2>0.70), minimum intercorrelation between the descriptors found in the same model (<0.5), Fischer ratio values and P values of 95% level of significance. A final set of QSARs was identified by applying cross-validation procedure following a "leave-one-out" technique with its predicting ability being evaluated and confirmed by cross validation coefficient Q^2 based on predictive error sum of squares (S_{PRESS}).

In the first step of regression analysis, correlation between each individual parameter and biological activity was calculated. The preliminary statistical treatment of the data revealed that multiparametric QSAR equations can be prevailed upon to account for the variance in the receptor antagonistic activity of triaryl imidazoles. Ample care was taken to avoid use of collinear variables in the same equation as it leads to spurious correlations. To confirm the absence of multicollinearity in the selected correlations, variance inflation factor (VIF) values were calculated for each parameter in the regression. VIF value was calculated from $1/1-R^2$, where R^2 is the squared multiple correlation coefficient of one parameter's effect regressed on the remaining parameter. VIF values greater than five indicate presence of unacceptably large multicollinearity between parameters in the correlation. The best models generated are summarized below alongwith the statistical parameters.

$$pIC_{50}=[2.046\ (\pm0.899)]+\log P(o/w)[0.725\ (\pm0.176)]+glob[5.687\ (\pm2.994)]$$
$$N=29,\ R=0.92,\ R^2=0.85,\ SEE=0.38,\ F=76.9,\ P<0.001,\ Q^2=0.82,\ S_{PRESS}=0.42,\ S_{DEP}=0.39 \quad (1)$$

$$pIC_{50}=[4.466\ (\pm1.214)]+KierA2[0.415\ (\pm0.136)]+PEOE\_VSA\_FNEG[-0.048\ (\pm0.024)][9.709\ (\pm6.373)]E\_OOP$$
$$N=29,\ R=0.92,\ R^2=0.85,\ SEE=0.39,\ F=46.4,\ P<0.001,\ Q^2=0.77,\ S_{PRESS}=0.49,\ S_{DEP}=0.46 \quad (2)$$

$$pIC_{50}=[5.404\ (\pm0.836)]+std\_dim3[1.813\ (\pm0.674)]+a\_nF[-0.746\ (\pm0.365)]+DASA[-0.005\ (\pm0.004)]$$
$$N=30,\ R=0.91,\ R^2=0.83,\ SEE=0.43,\ F=41.5,\ P<0.001,\ Q^2=0.76,\ S_{PRESS}=0.50,\ S_{DEP}=0.174 \quad (3)$$

In the above QSAR models N is the number of data points, R is multiple correlation coefficient, R^2 is squared correlation coefficient, SEE is standard error of estimate, F represents Fischer ratio between the variances of calculated and observed activities, figures given in the parentheses with $\pm$ sign in the model 95% confidence limits, P-value is the significance level of the regression, q^2 is cross validated squared correlation coefficient, S_{PRESS} and S_{DEP} correspond to standard deviation based on predicted residual sum of squares and standard deviation of error of prediction respectively. The Z-score method was adopted for the detection of outliers. Z-Score can be defined as absolute difference between the value of the model and the activity field, divided by the square root of the mean square error of the data set. Any compound which shows a value of Z-score higher than 2.5, during generation of a particular QSAR model was defined as an outlier.

As it can be seen, all the QSARs manifest good statistics and accounts for about 85% of the total variance in the glucagon antagonistic activity of triaryl imidazoles. The Fischer ratio values obtained for the QSARs exceed the tabulated value by a large margin as desired for a meaningful correlation. Cross-correlation analysis (Table 4) of the descriptors in the QSAR equations showed that all pair wise correla-

Table 2. Descriptor Used for Modeling Glucagons Receptor Antagonistic Activity of Triaryl Imidazole

Compound number	$-\log IC_{50}$	a_nF	KierA2	logP(o/w)	E_oop	DASA	std_dim3	glob	PEOE_VSA_FNEG
1	6.568636	1	6.035568	5.195	0.011552	13.26309	0.814417	0.054222	0.582677
2	5.853872	1	6.035568	5.232	0.01172	11.21578	0.820955	0.055952	0.582677
3	6.39794	1	5.760028	4.989	0.011612	37.33833	0.812918	0.054323	0.559775
4	5.69897	2	5.339163	4.55	0.011272	77.59695	0.813942	0.055101	0.525491
5	6.29243	1	6.280489	5.587	0.012453	0.282032	0.815381	0.054019	0.585545
6	5.886057	1	5.386189	4.695	0.027473	119.6537	0.816299	0.043368	0.532863
7	6.154902	1	6.168563	5.54	0.012278	102.9825	0.971066	0.046828	0.531907
8	5	1	6.560019	6.357	0.013911	126.0271	0.965787	0.038894	0.577478
9	5.69897	1	5.386189	3.725	0.010425	154.9307	0.803094	0.044838	0.492166
10	4.886057	1	5.920859	4.353	0.009805	130.4915	0.808057	0.038956	0.452291
11	5.09691	1	5.526891	4.057	0.014274	87.47182	0.806225	0.047926	0.511982
12	5.060481	1	6.460624	4.338	0.014522	115.1589	0.772062	0.029483	0.462583
13	5.657577	1	6.008662	4.937	0.013828	25.18064	0.832248	0.064083	0.548941
14	5.552842	1	6.008662	4.761	0.012516	31.09436	0.833341	0.064746	0.541815
15	5.823909	1	5.730389	5.617	0.014633	104.7471	1.201693	0.104857	0.561196
16	6.309804	1	6.350695	4.989	0.016565	89.28497	0.897208	0.047717	0.553318
17	6.106793	0	5.991556	5.042	0.012113	39.82599	0.804789	0.053187	0.59176
18	5.958607	1	6.150714	5.285	0.011271	28.06132	0.987042	0.074336	0.587287
19	6.721246	0	6.353393	5.428	0.011807	3.276122	0.813298	0.054064	0.591296
20	6.886057	0	6.908483	6.026	0.012602	35.83029	0.808814	0.053168	0.61461
21	6.853872	0	7.1285	6.796	0.013319	82.26358	1.008218	0.05165	0.603991
22	6.886057	0	6.694915	6.335	0.012772	53.63269	0.953897	0.052265	0.570173
23	7.130768	0	7.685489	6.493	0.012624	61.50308	0.99248	0.052586	0.557224
24	7.21467	0	7.1285	6.833	0.011604	56.70727	1.144189	0.074881	0.603991
25	8.187087	0	7.685819	6.444	0.129999	82.55631	1.675607	0.205301	0.576183
26	7.886057	0	7.685819	6.483	0.055925	69.71398	1.337133	0.115404	0.576183
27	7.568636	0	7.685819	6.446	0.073715	84.38068	1.108043	0.061471	0.576183
28	8.070581	0	8.29409	6.187	0.017877	48.47052	1.78578	0.290207	0.514574
29	7.886057	0	9.773677	6.693	0.01451	53.87344	1.643086	0.157266	0.477387
30	8.187087	0	11.07249	7.577	0.019523	48.26671	1.592539	0.128549	0.479378

Table 3. Descriptor Used for Selectivity Study for the Glucagon Receptor over p38 MAP Kinase

Compound number	Selectivity	SMR	VSA_HYD
1	−0.22724	10.17197	272.1161
2	−0.97004	10.17197	272.1161
3	−0.69897	9.86457	260.3408
4	−1.30103	9.39007	247.1685
5	−0.70757	10.68127	276.2692
6	−1.1597	9.80327	257.8561
7	−0.39794	10.73847	289.473
8	−1.52288	11.87317	309.6986
9	−1.45593	9.77081	226.2391
10	−2.11394	9.98477	261.8975
11	−1.58087	9.80107	248.7471
12	−1.4624	10.46352	264.106
13	−1.30103	9.95967	264.2119
14	−1.44716	9.95967	264.2119
15	−0.64461	11.08017	278.0816
16	−0.61101	10.50777	281.5688
17	−1.29115	10.11147	266.9951
18	−1.74036	10.33827	269.4497
19	−0.91703	10.33907	273.513
20	0.032185	11.15577	289.4414
21	1.372386	12.34767	322.8708
22	0.985522	1	322.8708
23	1.363178	1	318.4537
24	1.228479	0.875	318.4537
25	0.966576	1	318.4537
26	2.266268	0.875	358.1536

tions are <0.5 indicating low collinearity and non-dependency of the descriptors on each other. Equation 3 refers to the entire data set of 30 compounds whereas Eqs. 1 and 2 describe the same set without the compound 8. Compound 8 behaved as an outlier in Eqs. 1 and 2 with Z-Score value of 2.6 and 2.8 respectively and therefore excluded during the formulation of corresponding QSARs.

Equation 1 was found to be the most important two-variable correlation for modeling the glucagons receptor antagonistic activity of triaryl imidazoles. The molecular descriptors incorporated into the model are logarithm of the octanol/water partition coefficient (logP(o/w)) and Globularity (glob). The descriptor logP(o/w) is a measure of overall hydrophobicity of the molecule and therefore the positive coefficient associated with this term implies that increase in the lipophilicity of the molecule will cause a corresponding increase in the glucagon receptor antagonistic activity of triaryl imidazoles. The second term glob[10] in the correlation is a 3D molecular descriptor that characterizes the shape of a molecule. The large positive coefficient of this descriptor in the equation highlights the significance of molecular shape in drug–receptor interaction.

Equations 2 and 3 are the best triparametric correlations generated for modeling glucagon antagonistic activity of triaryl imidazoles. Although these QSARs exhibit marginally inferior statistics than Eq. 1, they merit attention since they provide some interesting information regarding glucagon antagonistic activity of triaryl imidazoles.

Equation 2 comprises of three descriptors, topological descriptor Kier's alpha modified shape index of second order,

Table 4. Correlation Matrix for Glucagons Receptor Antagonistic Activity of Triaryl Imidazole

	$-\log IC_{50}$	a_nF	KierA2	logP(o/w)	E_oop	DASA	std_dim3	glob	PEOE_VSA_FNEG
$-\log IC_{50}$	1								
a_nF	−0.776	1							
KierA2	0.79	−0.68	1						
logP(o/w)	0.789	−0.736	0.804	1					
E_oop	0.493	−0.337	0.267	0.304	1				
DASA	−0.312	0.222	−0.157	−0.236	0.139	1			
Std_dim3	0.783	−0.551	0.804	0.685	0.491	−0.001	1		
glob	0.677	−0.426	0.588	0.446	0.434	−0.132	0.905	1	
PEOE_VSA_FNEG	−0.709	0.894	−0.495	−0.724	−0.26	0.37	−0.425	−0.341	1

partial charge descriptor PEOE_VSA_FNEG, and potential energy descriptor E_OOP. The contribution of each individual descriptors to the QSAR as indicated by their corresponding regression coefficients can be given as E_OOP> KierA2>PEOE_VSA_FNEG. The topological descriptor KierA2[12] encodes information related to the degree of star graph-likeness and linear graph-likeness and takes a large value for a more linear molecule. Thus, the positive coefficient of the descriptor suggests that nonbranched molecules will have enhanced glucagon receptor affinity. The partial charge descriptor PEOE_VSA_FNEG represents the group contribution of vander Waals surface area of atoms with fractional negative charge in the molecule[11] and partial charge associated with each atom is calculated partial equalization of orbital electronegativities (PEOE) method.[13] The negative sign of the coefficient of this descriptor indicates increase in the fractional negative vander Waals surface area of the molecule is detrimental to the glucagon receptor antagonistic activity of triaryl imidazoles. The last descriptor in the equation is E_OOP,[11] which represent out-of-plane potential energy. The descriptor bears a positive coefficient in the equation, thus increase in the magnitude of E_OOP will contribute to increase the glucagon receptor affinity of the triaryl imidazoles.

Equation 3 includes two 3D descriptors std_dim3, DASA and an atom count descriptor a_nF and the contribution of the descriptors to the QSAR is given by the order std_dim3> a_nF>DASA. A standard dimension is equivalent to the standard deviation along a principal component axis. Standard dimension 3 is mathematically defined as the square root of the third largest eigenvalue of the covariance matrix of the atomic coordinates and is based on the both the structure connectivity and conformation of the molecule.[11] The positive coefficient of the descriptor suggests that geometric factors are of importance for the biological activity of triaryl imidazoles under study. The conformation dependent charge descriptors DASA represent absolute value of the difference between water accessible surface area of all atoms with positive partial charge and water accessible surface area of all atoms with negative partial charge.[11] The regression coefficient of the descriptor bears a negative sign, which suggest the minimal the difference in the water accessible surface area of all atoms with positive partial charge and water accessible surface area of all atoms with negative partial charge, the larger the glucagon antagonistic activity. The term a_nF denotes the fluorine atom in the molecule and from its negative coefficient in the model it appears that an increase in the fluorine atoms leads to decreased glucagon antagonistic activity.

From the regressions discussed so far, one may conjecture that hydrophobic and geometric factors predominantly govern the glucagon receptor affinity of the triaryl imidazoles under study. Furthermore, the correlations also indicates no definite role for electrostatic factors in the molecule–receptor interaction, a fact reflected in the negative contribution of partial charge descriptor PEOE_VSA_FNEG and positive contribution of the descriptor DASA which advocates for minimal difference in the water accessible surface area of all atoms with positive partial charge and water accessible surface area of all atoms with negative partial charge for improved glucagon receptor inhibitory potency. Additionally, the preponderance of descriptors representing molecular geometry emphasize on the likelihood of shape specific steric interactions between the triaryl imidazole derivatives and receptor. Surprisingly, compound number 8, which was found to be a statistical outlier in case of models 1 and 2 quietly, fits into the dataset for model 3. The phenomenon indicates that the 3D geometry descriptors are better placed in describing the variance in the glucagon receptor antagonistic activity of triaryl imidazoles.

It is worth mentioning that all the generated regressions exhibits good predictive ability as established by high q^2 values (>0.7) and the best being recorded for Eq. 1 ($q^2=0.8$). Further confirmation on the predictive ability is availed form the PRESS statistics of the QSARs, the uncertainty in the prediction (S_{PRESS}) and standard error due to prediction (S_{DEP}), which was less than 0.6. Besides the validation made by the leave-one-out procedure, the generated correlations were also tested for the ability to reproduce $-\log IC_{50}$ values of the compounds in the series and a comparison was made with observed values (Table 5). A good agreement between experimental data and model computation is achieved using the models 1—3 as shown in Figs. 1—3.

In addition to potent glucagon antagonistic activity, it is still desirable for triaryl imidazoles to maintain a good degree of selectivity for glucagon receptor over p38 mitogen activated protein kinase (MAP Kinase). In the view of above, the present study was extended for finding structural features contributing to the selectivity for the glucagon receptor over p38 MAP kinase. QSARs were constructed using selectivity ratio Y [where $Y=\log(1/IC_{50}(\text{glucagon receptor}) - \log(1/IC_{50}(\text{p38 MAP kinase}))$] as dependent variable and the calculated parameters as predictor variables (Table 3). Only 26 compounds were employed for the deduction of

Table 5. Predicted Glucagons Receptor Antagonistic Activity of Triaryl Imidazole by QSAR Models

Compound number	$-\log IC_{50}$	Model 1	Model 2	Model 3
1	6.568636	6.10142	5.93314	5.99038
2	5.853872	6.17031	5.97058	6.12279
3	6.39794	5.95106	5.81761	5.89531
4	5.69897	5.65505	4.96474	4.70522
5	6.29243	6.40892	6.06386	6.10308
6	5.886057	5.68375	5.84478	5.46217
7	6.154902	6.33765	6.01961	5.85493
8	5	—	—	5.84274
9	5.69897	4.86105	5.32455	5.18732
10	4.886057	5.47662	5.83619	5.52454
11	5.09691	5.28281	5.82494	5.69685
12	5.060481	5.38969	5.568	5.49904
13	5.657577	6.00698	5.98994	6.07582
14	5.552842	5.88588	5.98201	6.04884
15	5.823909	6.75621	5.86899	6.34646
16	6.309804	5.91515	6.13571	5.78477
17	6.106793	5.99915	6.5938	6.75466
18	5.958607	6.31376	6.01093	6.33886
19	6.721246	6.27055	6.66159	6.89481
20	6.886057	6.70575	6.90982	6.64383
21	6.853872	7.33946	7.02201	6.79219
22	6.886057	6.94123	6.81238	6.84706
23	7.130768	7.04309	7.24159	6.85289
24	7.21467	7.45496	6.96418	7.1771
25	8.187087	7.79959	8.40779	7.95959
26	7.886057	7.36541	7.48608	7.4208
27	7.568636	7.01907	7.73623	6.90477
28	8.070581	8.35549	7.34282	8.5102
29	7.886057	7.78019	7.87263	8.14953
30	8.187087	8.29092	8.76524	8.0061

QSARs as the remaining 4 compounds did not exhibit a well defined activity against p38 MAP kinase. Compound 8 behaved as an outlier because the Z-Score value greater than 2.5 therefore excluded during the formulation of corresponding QSARs. The best linear regressions generated are summarized below.

$$Y=[-10.686\ (\pm 1.753)]+\mathrm{VSA\_HYD}[0.036\ (\pm 0.006)]$$
$$N=25,\ R=0.93,\ R^2=0.86,\ SEE=0.44,\ F=147.5,\ p<0.00,\ Q^2=0.83,$$
$$S_{PRESS}=0.48,\ S_{DEP}=0.46 \quad (4)$$

$$Y=[-11.470\ (\pm 1.839)]+\mathrm{SMR}[1.021\ (\pm 0.169)]$$
$$N=25,\ R=0.93,\ R^2=0.87,\ SEE=0.43,\ F=155.2,\ p<0.00,\ Q^2=0.85,$$
$$S_{PRESS}=0.46,\ S_{DEP}=0.45 \quad (5)$$

The statistical measures of the equations summarized above portray their statistical significance and the validation parameters given alongwith strongly supports predictive potential of the selected QSARs. Equation 3 shows that the most prominent descriptor contributing for selectivity of triaryl imidazole for glucagon receptor is pharmacophore feature descriptor VSA_HYD.[11] VSA_HYD represents the approximate sum of vander Waals surface area of hydrophobic atoms hence the positive coefficient of the descriptor indicates that increase in the hydrophobic molecular surface area will render the molecules selective for glucagon receptor.

Another correlation with physicochemical descriptor SMR was also derived for the abovementioned dataset. SMR denotes molecular refractivity as defined by atomic contribution model of Crippen *et al.*[14] The term SMR is a crude measure of the bulk and polarizability of the molecule. The regression coefficient of the descriptor SMR bears a positive sign, which suggest that molecular bulk and polarizability are important determinants of selective inhibition of glucagon receptor by triaryl imidazoles. It becomes very much evident from generated QSARs that the structural properties of triaryl imidazole congeners such as hydrophobicity and steric properties which influence their glucagon receptor inhibitory activity also contribute to the selectivity for the inhibition glucagon receptor over p38 MAP kinase.

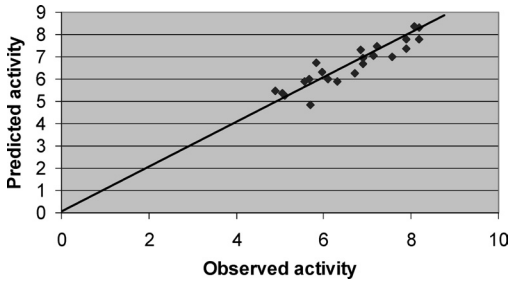


Fig. 1. Graphical Representation of Experimentally Observed *vs.* Computationally Predicted Activity of Model 1

Observed activity: biological activity, which was determined experimentally by selective inhibition of glucagon receptor. Predicted activity: biological activity, which was determined computationally from the selected regression models.

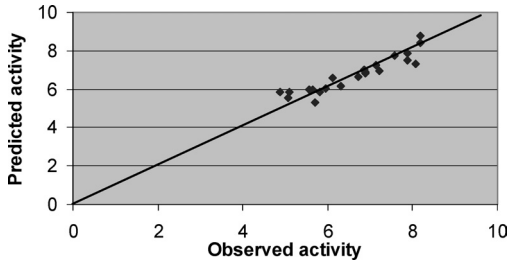


Fig. 2. Graphical Representation of Experimentally Observed *vs.* Computationally Predicted Activity of Model 2

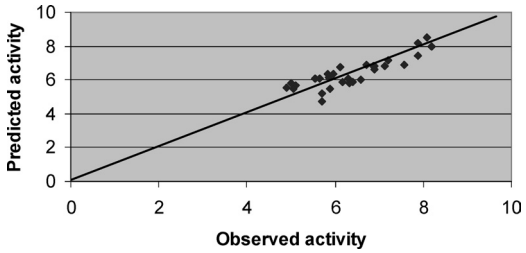


Fig. 3. Graphical Representation of Experimentally Observed *vs.* Computationally Predicted Activity of Model 3

Conclusion

In conclusion, the present study gives rise to QSARs with good predictive capacity for glucagon antagonistic activity of triaryl imidazoles. For the dataset of 30 triaryl imidazole derivatives with well-defined glucagon receptor antagonistic activity, hydrophobic and steric property of the molecules appears to be the governing factor for glucagon receptor inhibitory potency. Though electrostatic forces seem to be of less importance, its role in the ligand–receptor binding is detrimental as suggested by their negative contribution in the QSARs. Further, the results of the study also indicate that the

nature of interaction between the glucagon receptor and triaryl imidazoles is shape specific. Additionally, selectivity studies based on the QSARs generated with logarithm of ratio between the IC_{50} values triaryl imidazoles p38 MAP kinase and glucagon receptor suggest that the same structural features which influence the glucagon receptor affinity might also contribute to the selective inhibition of glucagon receptor over p38 MAP kinase by triaryl imidazoles.

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