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2D QSAR Study For 1-Aryloxy-3-(N^4-Piperazinyl) Propan-2-OLS

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ABSTRACT

Last three decades enormous work has been carried out on computational chemistry. The projects given for discovery of New Chemical Entities by these methods and gets a safe, potent drug molecule. However, the commercial output for the pharmaceutical company with these methodologies is negligible. Most of the drugs discovered in medicinal chemistry are accidentally. Thus synthesis of focused compound libraries and their pharmacological screening by efficient methods becomes powerful tool for drug discovery. But some additional points are required to move towards aryloxypropanolamines As 1-Aryloxy-3-(N^4-substituted piperazinyl) propan-2 OLS (aryloxypropanolamines) shows β-adrenergic receptor antagonist activity (β-blockers), these chemical entities are applicable in management of various diseases due to their therapeutic effects. The main clinical indications of β-blockers are in the area of cardiovascular diseases, such as hypertension, angina pectoris, myocardial infarction and cardiac arrhythmias[1-4]. However, some β-blockers readily access the brain because of their lipophilicity and can influence some central nervous system functions. Therefore, Propranolol has been used for the treatment of anxiety syndromes, prophylaxis of migraine headaches, schizophrenia, alcohol withdrawals and tremors[5-8.] Looking at the biological profile of various aryloxypropanolamines (also Enciprazine) molecule, synthesis of various derivatives of Enciprazine having different aryloxy moiety and amine moiety (by taking different N- alkyl/aryl substituted piperazine) was planned to get safe, potent or new activity molecules.

Keywords: QSAR, Principles of QSAR, QSAR models, QSAR model Validation

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INTRODUCTION

QSAR STUDY

Introduction to Quantitative Structure-Activity Relationships (QSAR)

Due to the demand for safer chemicals in medical and agricultural disciplines, scientists and engineers have been working over the last 20 years to design substances based on mitigating toxic effects on the ecological and human environment. A principle component of achieving this goal has involved rational molecular design strategies[9-11]. These methodologies were first implemented in pharmaceutical and drug design, but in the last decade, they have emerged in areas of bioremediation and engineering risk assessment applications.

QSARs are largely exploited by industries to expeditiously predict the biological/chemical activity and reactivity of organic compounds in the environment and engineered systems based on structural-congeneric compounds of known activity and reactivity. These algorithms assist in elucidating the reaction mechanisms and pathways of organic contaminants in the environment and accordingly, metabolites can be identified. Thus, the purpose of this section is to describe the nature and benefits of QSARs for understanding and predicting the behavior of xenobiotic chemicals.

A compound's chemical structure refers to the physical constitution of a molecule of the compound. This molecular structure is represented, in the first instance, by its *molecular graph* – a graph in the mathematical sense comprising a collection of vertices (denoting atoms in the molecule) connected by edges (chemical bonds between the atoms), capturing the topological structure of the molecule.

In a QSAR study, modeling is the dependence of activity upon chemical structure typically involves some form of regression analysis. A 'training collection' of chemical compounds (whose activity values are known) is the principal input into the modeling process, which proceeds by extracting its trends in the relationship between chemical structure and activity. The aspiration is for these trends to generalize to other chemical compounds beyond those occurring in the training set, thereby allowing predictions to be made about the activity of new (as yet unmeasured) chemical compounds based solely on knowledge of their chemical structure.

This QSAR modelling approach is underpinned by the so-called 'Fundamental Assumption of QSAR, that chemical compounds with similar chemical structures will have similar activities[12]. This assumption is a prerequisite both for the meaningful description of trends within the training set, and for the interpolation of those trends to encompass other compounds.

Underlying Principles of QSARs

QSARs predict the functions of a congeneric series of compounds by attempting to statistically correlate its functions to structural molecular characteristics and properties (*i.e.* descriptors). For purposes of this discussion, we refer structure to the molecular characteristics, activity to chemical or biological effects (substitution, toxicity, biotransformation), and property to environmental fate characteristics such as solubility, volatility, Henry's constant, etc[13]. The main assumptions in the QSAR approach when used in predicting biological fate is that \the factors governing the events in a biological system are represented by the descriptors characterizing the compounds, whose biological activity is expressed via the same mechanism" and all physical, chemical, and biological properties of a chemical substance can be computed from its molecular structure, encoded in a numerical form with the aid of various descriptors"[14]. Similar assumptions are made regarding behavior in a biotic chemical reactions.

QSAR Model

QSAR algorithms are multivariate mathematical relationships between a set of descriptors (properties or structural), *xij*, and a chemical or biological activity, *yi*. For compound i, the linear relationship relating descriptors, *xi*1, *xi*2 to activity, *yi*, is as follows:

$$yi = xi1m1 + xi2m2 + + xinbn + ei$$

where, m is the linear slope expressing the correlation between property *xij* with activity *yi* of compound i, and *ei*is a constant. Typically, the slopes and *ei* are found through regression analyses such as simple linear regression (SLR), multiple linear regression (MLR), variant MLR (stepwise MLR), partial least squares, and principal component analysis (PCA) [14].

QSAR Model Validation

The validity of the QSAR model chosen is dependent on several criteria. The following list summarizes these requirements:

- Biological or chemical activity must relate to physic-chemical properties
- Chemical activities must be based on same mechanism
- Congeneric chemicals should be used in analyses

These guidelines assist in the selection of the appropriate chemical sets. As stated previously, the series of compounds must exhibit a specific activity through a common mechanism that can be modelled by a QSAR equation.

Overview of QSAR:

QSAR models are built according to an inductive machine learning formulation. The modelling

process begins with a 'training set' of chemical compounds whose chemical structure and biological activities are known, and proceeds by performing some sort of regression analysis to construct a predictive model of activity as a function of structure.

QSAR studies are therefore underpinned by the assumption that chemical compounds with similar structures have similar activity values; this shall be referred as the Fundamental Assumption of QSAR[12]. Quite how this Fundamental Assumption of QSAR is applied, however, depends on precisely how it is judged what constitutes similarity of chemical structures.

The 2D QSAR study was carried on Series-I (GG_{1-36}). For this purpose, sixcompounds were randomly selected as Test set for QSAR Model building and remaining 30 compounds were selected as Training set for validation of QSAR Model. The QSAR results obtained were given as below.

Results of 2D QSAR: (anxiolytic activity)

The QSAR model was build up using multiple regression method in conjunction with the stepwise variable selection method in Vlife MDS 4.2. The generated model is able to classify anxiolytic activity variation ~77 % (r^2 = 0.77) and ~60 % (Pred_r^2 = 0.59) variation in the test set indicating the predictive ability of model to be good. The robustness of the model was evaluated using the Leave one out cross validation (q^2 = 0.61). The fitness plot is as shown in Figure 1.

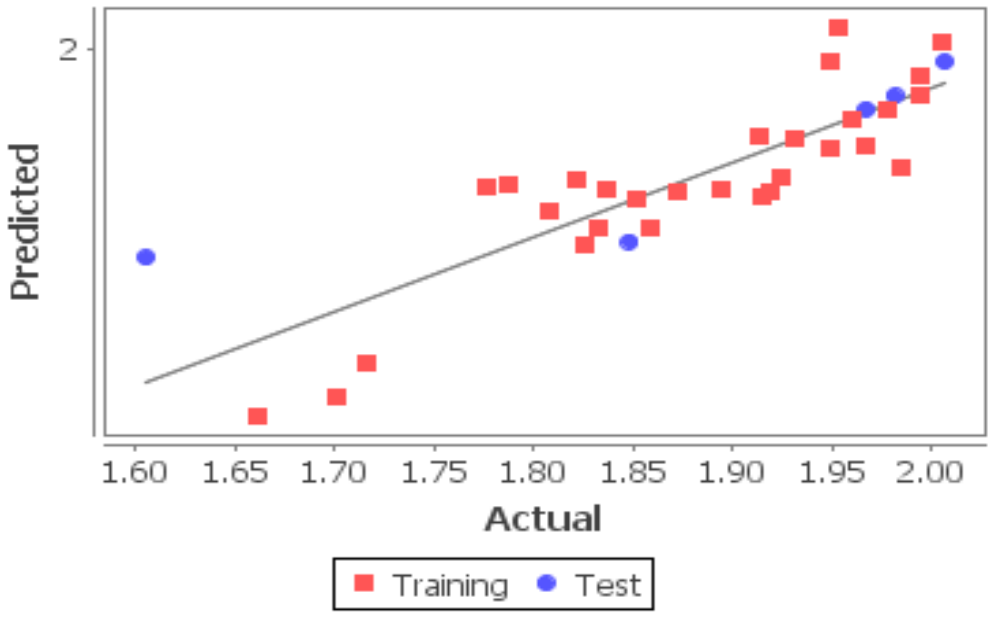

Figure 1: Fitness plot.

The parameters selected in the model are T_C_O_3, $SssCH_2$count, Epsilon R, SaaaCE-index, T_Cl_Cl_4, k3alpha suggest a good variation in the dataset and descriptors to generate new lead molecules. The most important descriptor is Epsilon R with 27% contribution as seen from the

contribution plot (Cf. Figure 2). The descriptor indicates that the electronegativity without considering the heteroatoms and multiple bonds in a molecule is conducive for the anxiolytic activity. Thus increasing the electronegativity of the compounds will lead to more active molecules.

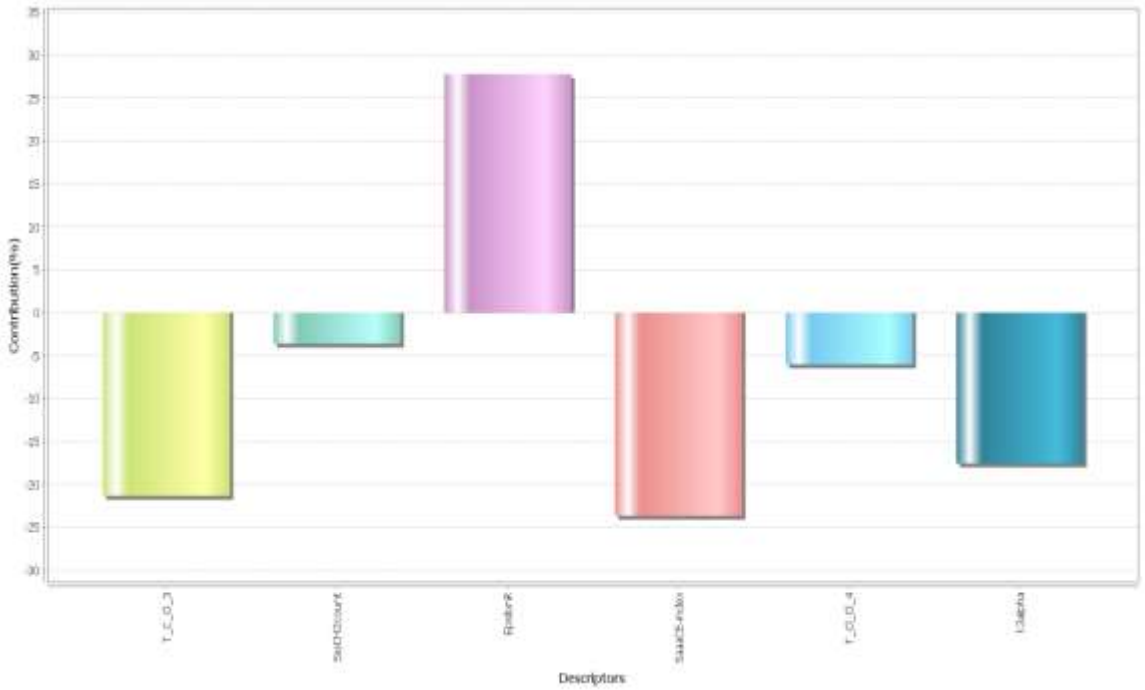

Figure 2: Contribution Plot

The second most important descriptor is SaaaCE-index which is the electro topological index of aromatic carbon which is attached to three heavy atoms (i.e. without Hydrogen). SaaaCE-index is (-23 %) is detrimental for biological activity suggests that more substitution on the aromatic carbon will reduce the biological activity.

The Third most contribution descriptor is T_C_O_3 which is the number of carbon atoms separated from oxygen atoms by three bonds. T_C_O_3 (-21%) is also detrimental for biological activity, suggesting presence of oxygen atoms close to carbon atoms (3 bond distance) will reduce the biological activity.

K3alpha contributes to -18% to the biological activity, the descriptor means third alpha modified shape index. Branching in the molecule is detrimental for the anxiolytic activity of the compounds. $SssCH_2$count and T_Cl_Cl_4 both are detrimental for activity (-3.6 and -6.0 % respectively). The descriptor terms suggest that having more CH_2 groups and multiple chlorine atoms will reduce the biological activity

Table 1: Indicating actual and predicted activity of training and test set compounds along with the residuals.

Training set	Actual	Predicted	Residual	Test set	Actual	Predicted	Residual
Cpd_GG$_{23}$_13_3D_opt.mol2	1.948	1.90993	0.03807	Cpd_GG$_{4}$_34_3D_opt.mol2	1.605	1.81331	-0.20831
Cpd_GG$_{22}$_11_3D_opt.mol2	1.915	1.86759	0.04741	Cpd_GG$_{36}$_4_3D_opt.mol2	1.981	1.95736	0.02364
Cpd_GG$_{8}$_19_3D_opt.mol2	1.913	1.92202	-0.00902	Cpd_GG$_{6}$_56_3D_opt.mol2	1.848	1.82787	0.02013
Cpd_GG$_{26}$_16_3D_opt.mol2	1.872	1.8726	-0.0006	Cpd_GG$_{35}$_3_3D_opt.mol2	2.006	1.98803	0.01797
Cpd_GG$_{7}$_18_3D_opt.mol2	1.776	1.87581	-0.09981	Cpd_GG$_{34}$_2_3D_opt.mol2	1.967	1.94601	0.02099
Cpd_GG$_{25}$_15_3D_opt.mol2	1.825	1.82558	-0.00058				
Cpd_GG$_{27}$_17_3D_opt.mol2	1.858	1.83935	0.01865				
Cpd_GG$_{9}$_20_3D_opt.mol2	1.984	1.89264	0.09136				
Cpd_GG$_{12}$_10_3D_opt.mol2	1.96	1.93625	0.02375				
Cpd_GG$_{24}$_14_3D_opt.mol2	1.787	1.87829	-0.09129				
Cpd_GG$_{33}$_72_3D_opt.mol2	1.994	1.95736	0.03664				
Cpd_GG$_{15}$_23_3D_opt.mol2	1.822	1.88222	-0.06022				

Training set	Actual	Predicted	Residual	Test set	Actual	Predicted	Residual
Cpd_GG$_{5}$_45_3D_opt.mol2	1.808	1.85469	-0.04669				
Cpd_GG$_{14}$_12_3D_opt.mol2	1.931	1.91982	0.01118				
Cpd_GG$_{13}$_1_3D_opt.mol2	1.918	1.8712	0.0468				
Cpd_GG$_{31}$_67_3D_opt.mol2	1.978	1.94601	0.03199				

Table 2: Table indication model statistics:

Model	r^2	q^2	r^2_se	q^2_se	F test	Pred r^2
Log10(Column)= -0.18 (T_C_O_3) -0.02 (SssCH2count) + 0.08 (EpsilonR) -0.14 (SaaaCE-index) -0.08 (T_Cl_Cl_4) -0.16 (k3alpha) + 1.4659	0.77	0.61	0.04	0.06	12.54	0.59

External set prediction:

A set of 36 (GG_{37-72}) molecules of Series-II was taken for the prediction of Anxiolytic activity based on the QSAR model generated. To check the reliability of the predictions extrapolation was calculated, the extrapolation value more then 3/2 times the r^2_SE (i.e. 3/2 * 0.04 = 0.06) is unreliable.

The predictions are as indicated in table 3.

Table 3: External Set Predictions

Compound	T_C_O_3	SssCH2 Count	EpsilonR	SaaaCE- Index	T_Cl_Cl_4	k3alpha	Pred	Extpoln	Actual Activity
Cpd_GG_{49}	3	6	28.8	0	0	5.031	2.375	0	237.1374
Cpd_GG_{50}	3	6	28.8	0	0	5.288	2.334	0	215.7744
Cpd_GG_{51}	3	6	28.8	0	0	5.288	2.334	0	215.7744
Cpd_GG_{40}	4	6	30.1	0	0	5.031	2.299	0.059	199.0673
Cpd_GG_{41}	4	6	30.1	0	0	5.27	2.261	0.059	182.3896
Cpd_GG_{42}	4	6	30.1	0	0	5.27	2.261	0.059	182.3896
Cpd_GG_{46}	3	6	30.1	0	0	5.27	2.447	0.059	279.8981
Cpd_GG_{47}	3	6	30.1	0	0	5.526	2.405	0.059	254.0973
Cpd_GG_{48}	3	6	30.1	0	0	5.526	2.405	0.059	254.0973
Cpd_GG_{43}	3	6	30.1	0	0	5.27	2.447	0.059	279.8981
Cpd_GG_{44}	3	6	30.1	0	0	5.526	2.405	0.059	254.0973
Cpd_GG_{45}	3	6	30.1	0	0	5.526	2.405	0.059	254.0973
Cpd_GG_{37}	5	6	31.1	0	0	5.272	2.159	0.144 #	144.2115
Cpd_GG_{38}	5	6	31.1	0	0	5.511	2.12	0.144#	131.8257
Cpd_GG_{39}	5	6	31.1	0	0	5.511	2.12	0.144#	131.8257
Cpd_GG_{67}	3	6	29.5	0	0	5.171	2.412	0.008	258.226
Cpd_GG_{68}	3	6	29.5	0	0	5.415	2.373	0.008	236.0478
Cpd_GG_{69}	3	6	29.5	0	0	5.415	2.373	0.008	236.0478
Cpd_GG_{70}	3	6	29.5	0	0	5.415	2.373	0.008	236.0478
Cpd_GG_{71}	3	6	29.5	0	0	5.677	2.33	0.008	213.7962
Cpd_GG_{72}	3	6	29.5	0	0	5.677	2.33	0.008	213.7962
Cpd_GG_{64}	3	6	30.2	0	1	5.574	2.319	0.068#	208.4491
Cpd_GG_{65}	3	6	30.2	0	1	5.823	2.279	0.068#	190.1078
Cpd_GG_{66}	3	6	30.2	0	1	5.823	2.279	0.068#	190.1078
Cpd_GG_{52}	3	6	30.2	0	1	5.34	2.357	0.068#	227.5097
Cpd_GG_{53}	3	6	30.2	0	1	5.574	2.319	0.068#	208.4491
Cpd_GG_{54}	3	6	30.2	0	1	5.574	2.319	0.068#	208.4491
Cpd_GG_{55}	4	6	33.7	0	0	6.366	2.389	0.364#	244.9063
Cpd_GG_{56}	4	6	33.7	0	0	6.65	2.343	0.364#	220.2926

Compound	T_C_O_3	SssCH2 Count	EpsilonR	SaaaCE- Index	T_Cl_Cl_4	k3alpha	Pred	Extpoln	Actual Activity
Cpd_GG_{57}	4	6	33.7	0	0	6.65	2.343	0.364#	220.2926
Cpd_GG_{58}	4	6	33.4	2.249	0	4.737	2.289	0.338 #	194.536
Cpd_GG_{59}	4	6	33.4	2.248	0	4.921	2.26	0.338 #	181.9701
Cpd_GG_{60}	4	6	33.4	2.247	0	4.921	2.26	0.338 #	181.9701
Cpd_GG_{61}	3	6	33.4	2.357	0	4.921	2.43	0.338 #	269.1535
Cpd_GG_{62}	3	6	33.4	2.356	0	5.116	2.399	0.338 #	250.6109
Cpd_GG_{63}	3	6	33.4	2.355	0	5.116	2.399	0.338 #	250.6109

# indicates unreliable predictions.

The predictions indicate that most of the compounds which fall within the applicability domain are active compounds.

Discussion on QSAR Study:

The results obtained from 2D QSAR for our Series-II indicate that compounds GG_{40-51} and GG_{67-72} were shown reliable predictions which may be active as anxiolytic agent, while compounds GG_{37-39} and GG_{52-66} were shown unreliable predictions and were may not active as anxiolytic agent.

2D QSAR study of synthesized compounds for antihypertensive activity:

Biological activity:

The biological activity of the compounds from the Tail Cuff Technique was converted to IC50 by scaling up the test concentration with respect to the standard and calculating the concentration required to obtain 50% of the response of the standard compound.

QSAR Analysis

The QSAR model was build up using multiple regression method in conjunction with the Stepwise variable selection method in Vlife MDS 4.2. The generated model is able to classify anxiolytic activity variation ~ 77 % (r2 = 0.77) and ~62 % (Pred_r2 = 0.62) variation in the test set indicating the predictive ability of model to be good. The robust ness of the model was evaluated using the Leave one out cross validation (q2 = 0.64). The fitness plot is as shown in figure 1. The QSAR model is indicated in table 1.

Table 4: Table indication model statistics

Model	r2	q2	r2_se	q^2_se	F test	Pred r^2
Log10(IC50)= 107.75 chiV6chain - 5.14 1PathCount + 9.54 AlphaR + 0.18 5PathCount - 0.12 T_C_O_6 - 4.76	0.77	0.64	0.10	0.13	13.41	0.62

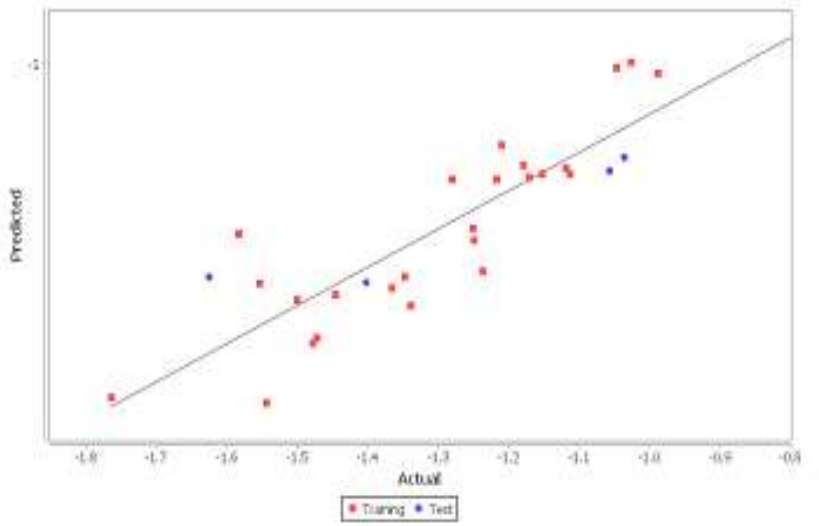

Figure 3: Fitness plot.

The parameters selected in the model are chiV6chain, 1PathCount, AlphaR, 5PathCount and T_C_O_6 suggest a good variation in the dataset and descriptors to generate new lead molecules. The most important descriptor is 1PathCount with -48% contribution as seen from the contribution plot (Cf. Fig 2). The descriptor indicates that the single path fragment in a molecule is detrimental for the antihypertensive activity. Thus decreasing or keeping low the number of atoms in the molecules compounds will lead to more active molecules.

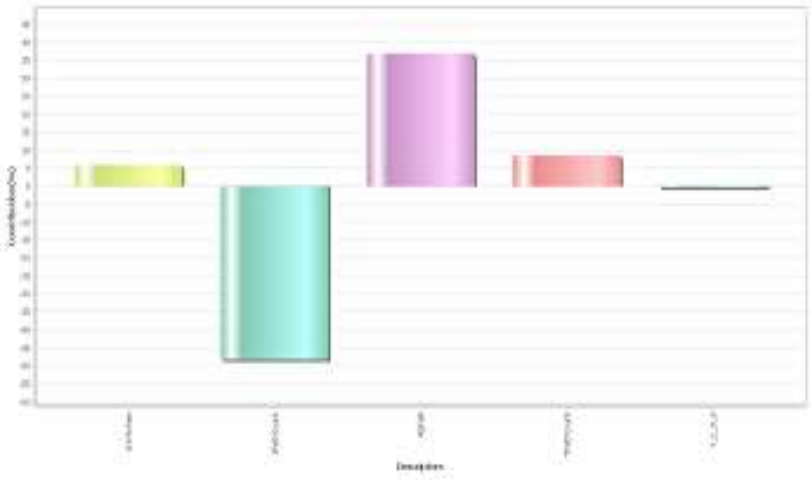

Figure 4: Contribution Plot

The second most important descriptor is AlphaR indicates sum of alpha value of all non-hydrogen atoms in a reference alkane. The reference alkane is when all heteroatoms in the molecular graph are replaced by carbon and multiple bonds are replaced by single bond, corresponding molecular graph may be considered as the reference alkane. AlphaR is (36 %) is Conducive for biological activity suggests that having more hydrogen atoms with respect to the total number of atoms increases activity.

The Third most contribution descriptor is 5PathCount descriptor which signifies total number of fragments of fifth order. 5PathCount (8.5%) is also conducive for biological activity, suggesting increasing the branching of the compounds is will increase the biological activity. chiV6chain contributes to 6 % to the biological activity, the descriptor atomic valence connectivity index for six membered ring. This suggests that the increasing the substitution on the six membered rings is detrimental for activity.

T_C_O_6 is detrimental for activity (-0.36 %). The descriptor terms suggest that having more Carbon atoms away from oxygen atoms at 6 bond distance will reduce the biological activity.

Table no.5 Indicating actual and predicted activity of training and test set compounds along with the residuals.

Table 5

Training set	Actual	Predicted	Residual	training set	Actual	Predicted	Residual
Cpd_29	-1.37	-1.41	0.04	Cpd_8	-1.63	-1.39	-0.23
Cpd_33	-1.03	-1.00	-0.03	Cpd_1	-1.04	-1.17	0.13
Cpd_24	-1.45	-1.42	-0.02	Cpd_30	-1.40	-1.40	0.00
Cpd_5	-1.48	-1.51	0.03	Cpd_35	-1.06	-1.20	0.14
Cpd_23	-1.50	-1.43	-0.07				
Cpd_17	-1.35	-1.39	0.04				
Cpd_9	-1.24	-1.38	0.14				
Cpd_6	-1.47	-1.50	0.03				
Cpd_31	-0.99	-1.02	0.03				
Cpd_14	-1.58	-1.31	-0.27				
Cpd_22	-1.34	-1.44	0.10				
Cpd_10	-1.22	-1.21	0.00				
Cpd_3	-1.21	-1.15	-0.06				
Cpd_34	-1.17	-1.21	0.04				
Cpd_15	-1.25	-1.30	0.05				
Cpd_11	-1.11	-1.20	0.09				
Cpd_7	-1.55	-1.40	-0.15				
Cpd_36	1.18	--1.19	0.01				
Cpd_32	-1.05	-1.01	-0.04				
Cpd_27	-1.76	-1.61	-0.15				
Cpd_13	-1.25	-1.32	0.07				
Cpd_12	-1.12	-1.19	0.07				
Cpd_20	-1.15	-1.20	0.05				
Cpd_26	-1.54	-1.62	0.08				
Cpd_19	-1.28	-1.21	-0.07				

External set prediction:

A set of 36 molecules was taken up for the prediction of Anti-hypertensive activity based on the QSAR model generated. To check the reliability of the predictions extrapolation was calculated, the extrapolation value more then 3/2 times the r^2_SE (i.e. 3/2* 0.04 = 0.06) is unreliable. The predictions are as indicated in table 6 below.

Table 6: External set prediction:

	chiV6chain	1PathCount	AlphaR	5PathCount	T_C_O_6	Prediction	Extrapolation
Cpd_37	0.11	26	12	61	4	-0.976	0.846#
Cpd_38	0.11	26	12	61	4	-0.976	0.846#
Cpd_39	0.11	26	12	61	4	-0.976	0.846#
Cpd_40	0.106	27	12.5	64	5	-1.359	0.015
Cpd_41	0.106	27	12.5	64	5	-1.359	0.015
Cpd_42	0.106	27	12.5	64	5	-1.359	0.015
Cpd_43	0.106	27	12.5	64	5	-1.239	0.015
Cpd_44	0.106	27	12.5	64	4	-1.239	0.015
Cpd_45	0.106	27	12.5	64	4	-1.239	0.015
Cpd_46	0.106	27	12.5	65	4	-1.05	0.015
Cpd_47	0.106	27	12.5	65	4	-1.05	0.015
Cpd_48	0.106	27	12.5	65	4	-1.05	0.015
Cpd_49	0.106	28	13	67	5	-1.16	-0.163#
Cpd_50	0.106	28	13	67	5	-1.16	-0.163#
Cpd_51	0.106	28	13	67	5	-1.16	-0.163#
Cpd_52	0.106	27	12.5	64	4	-1.239	0.015
Cpd_53	0.106	27	12.5	64	4	-1.239	0.015
Cpd_54	0.106	27	12.5	64	4	-1.239	0.015
Cpd_55	0.106	27	12.5	65	4	-1.05	0.015
Cpd_56	0.106	27	12.5	65	4	-1.05	0.015
Cpd_57	0.106	27	12.5	65	4	-1.05	0.015
Cpd_58	0.102	28	13	68	4	-1.251	-0.357#
Cpd_59	0.102	28	13	68	4	-1.251	-0.357#
Cpd_60	0.102	28	13	68	4	-1.251	-0.357#
Cpd_61	0.102	28	13	67	4	-1.44	-0.546#
Cpd_62	0.102	28	13	67	4	-1.44	-0.546#
Cpd_63	0.102	28	13	67	4	-1.44	-0.546#
Cpd_64	0.106	30	14	71	6	-1.259	-0.142#
Cpd_65	0.106	30	14	71	6	-1.259	-0.142#
Cpd_66	0.106	30	14	71	6	-1.259	-0.142#

Cpd_67	0.13	31	14	86	5	-0.849	0.147#
Cpd_68	0.13	31	14	86	5	-0.849	0.147#
Cpd_69	0.13	31	14	86	5	-0.849	0.147#
Cpd_70	0.13	31	14	85	5	-1.038	-0.042
Cpd_71	0.13	31	14	85	5	-1.038	-0.042
Cpd_72	0.13	31	14	85	5	-1.038	-0.042

# indicates unreliable predictions.

CONCLUSION:

The predictions indicate that most of the compounds which fall within the applicability domain are active compounds. The results obtained from 2D QSAR study for Series-II compounds indicate that compounds GG_{40-48}, GG_{52-57} and GG_{70-72} are found to have better predicted activity than the most active compound of the training set which may be active as antihypertensive agent. While compounds GG_{37-39}, GG_{49-51} and GG_{58-69} were shown unreliable predictions and were may not active as antihypertensive agent.

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