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2D-QSAR of Oxadiazolyl Ketones as DPP-IV Inhibitors

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Abstract: A quantitative structure–activity relationship (QSAR) study has been performed on Oxadiazolyl ketone based inhibitors of dipeptidyl peptidase IV (DPP-IV) and dipeptidyl peptidase II (DPPII) to understand the structural features influencing the affinity of these inhibitors towards the enzyme. The compounds in the selected series were characterized by physicochemical and fragmental descriptors calculated using 2D-QSAR module of VLife™ MDS software. Correlations between different inhibitory activities and calculated predictor variables were established through employing the simulated annealing method. The results of the study indicates that dipeptidyl peptidase IV and DPPII inhibitory activities of Oxadiazolyl ketone can be successfully explained in terms of physicochemical parameters of the molecule. The obtained correlations suggest that increase in the number of carbon atoms connected to four single bonds will augment inhibitory activity of these molecules against DPP-IV probably by virtue of carbon rotation in the active site of the enzymes. One of the prime electrotopological requirements for better inhibition of DPP-IV is that the compounds should have less number of oxygen atoms connected with one double bond. Besides electrotopological indices partition coefficient also positively contributes to DPP-IV inhibition. Improved DPPII inhibition may be achieved by reducing number of hydrogen atoms and rotatable bonds. It is due to flexibility of molecule, may hinder the binding of molecules to the enzyme active site. Better inhibition of both DPP-IV and DPPII may be accomplished by expanding molecular shape of the molecules for complimentary to the enzyme active site.
Keywords: DPP-IV, Oxadiazolyl, DPPII, Vlife.

Introduction:

GLP-1 (glucagon-like peptide 1) has been intensively studied as a treatment of type 2 diabetes mellitus (T2DM).[1] GLP-1 is an incretion hormone secreted by intestinal L-cells in response to food intake. This hormone plays several biological roles including the stimulation of insulin secretion, inhibition of glucagon secretion, retardation of gastric emptying, induction of satiety and stimulating the regeneration and differentiation of islet b cells.[2] However GLP-1 is rapidly degraded in plasma by the action of dipeptidyl peptidase IV (DPP-IV). DPP-IV is a serine protease cleaving the N-terminal dipeptide with a preference for L-proline or L-alanine at the penultimate position.[3] This protease is expressed in many tissues and body fluids, and exists as either a membrane-bound or a soluble enzyme. Inhibition of DPP-IV has been reported to increase the level of GLP1[4] which increases pancreatic b-cell proliferation and survival, thus raises insulin level which can ameliorate hyperglycemia in type 2 diabetes. For this reason, DPP-IV inhibitors are emerging as new potential drugs of T2DM,[5] with Sitagliptin(**1**)[6] already in the market. Extensive research has resulted in a series of potent DPP-IV inhibitors, and several DPP-IV inhibitors are under late-stage clinical development including Vildagliptin **2**[7] (Fig. 1). Recently, hundreds of compounds have been synthesized which were found to possess excellent DPP-IV inhibitory activity i.e.

pyrrolidine, thiazolidine, cyano-pyrrolidine, cyanothiazolidine, Piperidinyl-2-phenethylamino, .[8] 3D pharmacophore models have been generated by Wu *et al* using a training set of 22 DPP-IV inhibitors With the view of progression of design and development of novel inhibitors of DPP-IV, a quantitative structure–activity relationship (QSAR) study has been performed in order to relate DPP-IV inhibitory activity of these Oxadiazolyl ketones inhibitors to their molecular structures. Although structure based design has been used primarily in the design of new DPP-IV inhibitors, there are several examples where the indirect approaches such as QSAR have been utilized in search of more potent analogues.[9,10] QSAR analysis will provide structural insight into the mechanism of action of these inhibitors, which is of utmost importance in the design of new analogues by modification of structure of parent compound.

Material And Methods:

The QSAR study has been performed on a series of compounds Oxadiazolyl ketones, reported by Lee *et al*[13]. The biological activities of these 22 compounds were expressed in terms of IC_{50} values for inhibition of DPP-IV. All the IC_{50} values of the compounds were reported in terms of micromolar (μM) concentration. For correlation purposes, reported IC_{50} values were converted to their molar units and subsequently to free energy related negative logarithmic state, i.e. $-\log(1/IC_{50})$. All the computational studies were performed on Compaq (Pentium-D) computer using the software VLife™ MDS. Molecules were sketched using the same. Optimizations of the sketched compounds were done by batch minimization process using force field computations of the VLife™ MDS. Various 2D descriptors were calculated for optimized structures of the molecules using QSAR module of VLife™. A large number of descriptors were generated by the VLife™ (**Table 1**). The descriptor pool was reduced by eliminating out the descriptors with constant and near constant values. Further reduction in the descriptor pool was done by ousting the descriptors that are highly degenerate and the descriptors that were showing very low correlation with inhibitory activity. The remaining physicochemical descriptors were taken into account for the reported analysis. The series of compounds along with the descriptors used in the selected regressions are given in the **Table 2**. Data set generated so was subjected to statistical analyses. Stepwise multiple regression analysis was used as statistical tool, with the help of VLife™. The QSAR models were generated using biological activity as dependent variable and descriptors as independent variables. Correlations between different inhibitory activities and calculated predictor variables were established through simulated annealing method. QSARs generated for different inhibitory activity data were as follows:

Model 1 DPP-IV

Log $(1/IC_{50})$ = [10.4092] + SssssCE-index[0.2774] + k3alpha[0.3339] + SdOE-index[-0.1473] + XlogP[0.0960].

Training Set Size = 22 (100 %), N = 22, r = 0.8930, r2 = 0.7976, q2 = 0.6976, F test = 23.65, r2 se = 0.3189, q2 se = 0.3898

Model 2 DPP-II

Log $(1/IC_{50})$ = [7.2382] + RotatableBondCount[-0.2531] + kappa2[0.6673] + HydrogensCount[-0.1424].

Training Set Size = 16, N = 16, r = .8999, r^2 = 0.8099, q^2 = 0.6439, F test = 27.6886, r^2 se = 0.3828, q^2 se = 0.5238

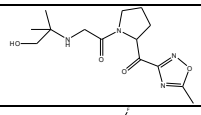
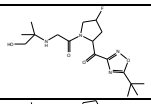
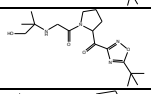
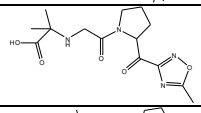
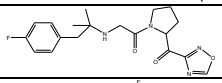
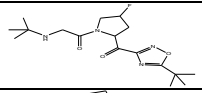
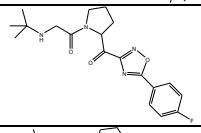
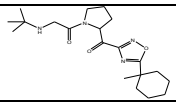
In the above QSAR models, N is the number of data points, r is correlation coefficient, r^2 is squared correlation coefficient which when multiplied by 100 gives explained variance in biological activity, q^2 is cross validated squared correlation coefficient, r^2_se is standard error of squared correlation coefficient, q^2_se is standard error of cross validated r^2, F test represents Fischer ratio between the variances of calculated and observed activities. All the QSAR models are significant at 99% level as shown by their Fischer ratio values, which exceed the tabulated values by a large margin as desired for a meaningful correlation. Each QSAR model can explain more than 75% of the total variance (r2 > 0.75) in the DPP inhibitory activity exhibited by Oxadiazolyl ketone derivatives, the highest and lowest r2 values of 0.8099 and 0.7976 were recorded for inhibition of DPP-II and DPP-IV. Accuracy in the analysis is shown by low values of standard error of squared correlation coefficient.

It is very much evident from the obtained correlations that the DPP inhibitory activity of Oxadiazolyl ketone can be successfully explained in terms of physicochemical parameters of the molecules. The observation also stems from the fact that physicochemical descriptors appear predominantly in all the regressions generated for describing DPP inhibitory activity of Oxadiazolyl ketones.

Table-1 Descriptors generated by the VLife.

Physicochemical descriptors	**Subclass of Physicochemical descriptors**
Individual	Volume, H-AcceptorCount, H-DonorCount, Rotatable Bond Count, XlogP, slogp, smr, polarizabilityAHC, polarizabilityAHP, Mol.Wt.
Retention index	chi0, chi1, chi2, chi3, chi4, chi5,
Atomic valence connectivity index	chiV0, chiV1, chiV2, chiV3, chiV4, chiV5.
Path count	0PathCount, 1PathCount, 2PathCount, 3PathCount, 4PathCount, 5PathCount.
Chi Chain	chiV5chain,
Chiv Chain	chiV6chain
Chain path count	chi5chain, chi6chain.
Cluster	chi4pathCluster, chiV3Cluster
Path Cluster	chi3Cluster, chiV3Cluster, 3ClusterCount, chi4pathCluster, chiV4pathCluster, 4pathClusterCount
Kappa	kappa1, kappa2, kappa3, k1alpha, k2alpha, k3alpha
Element count	HydrogensCount, CarbonsCount, OxygensCount, NitrogensCount, SsCH3count, SssCH2count, SaaCHcount, SaasCcount, SssOcount
Estate number	SsCH3E-index, SssCH2E-index, SaaCHE-index, SaasCE-index, SaaNHE-index, SaaNE-index, SsssNE-index, SsOHE-index, SssOE-index.
poplar surface area	PolarSurfaceAreaExcludingPandS, PolarSurfaceAreaIncludingPandS.

Table-2 Compounds along with the selected descriptors used in models.

Compounds	**Structures**	**SssssCE-index**	**k3alpha**	**SdOE-index**	**XlogP**	**RotatableBondCount**	**kappa2**	**HydrogensCount**
10a		-0.54	4.05	24.72	-0.481	11	7.71	22
10b		-1.07	5.01	25.16	0.974	14	8.57	27
10c		-0.89	4.78	25.20	1.302	14	8.35	28
10d		-1.22	3.94	35.76	-0.279	11	7.92	20
10e		-0.36	4.91	25.13	2.093	10	9.67	23
10f		-0.64	4.99	25.11	2.201	13	7.94	27
10g		-0.19	4.71	25.31	2.479	10	9.21	23
10h		-0.28	4.70	25.55	3.535	11	8.79	32

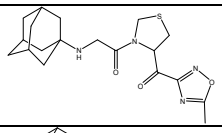
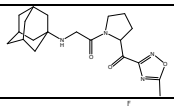
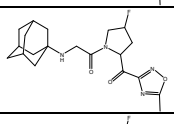
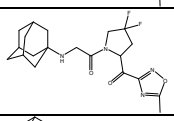
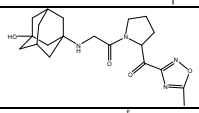
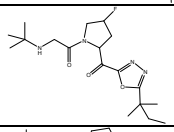
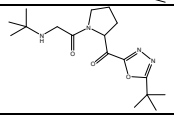
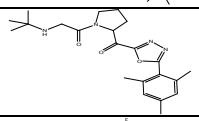
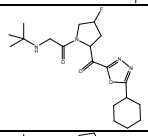
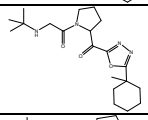
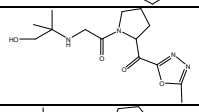
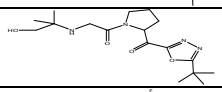
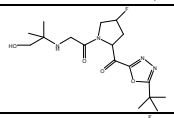
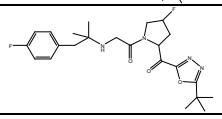
13a		0.18	3.30	25.71	3.214	7	7.36	26
13b		0.16	3.19	25.64	1.871	7	7.36	28
13c		0.06	3.39	25.60	1.543	7	7.60	27
13d		-3.15	3.57	25.55	2.091	7	7.55	26
13e		-0.68	3.29	25.67	0.823	8	7.30	28
18a		-0.60	5.03	25.23	3.246	14	8.57	29
18b		-0.46	4.79	25.14	3.124	13	7.71	28
18c		-0.17	4.86	25.65	3.815	13	9.65	30
18d		-0.24	5.06	25.34	2.865	10	9.21	29
18e		-0.28	4.70	25.54	4.13	11	8.79	32
18f		-0.54	4.05	24.70	0.114	11	7.71	22
18g		-0.89	4.78	25.19	1.897	14	8.35	28
18h		-1.07	5.01	25.15	1.569	14	8.57	27
18i		-0.91	6.13	25.78	4.314	14	10.73	30

Table-3 Actual and predicted activity values.

COMPOUNDS	DPP-IV		DPP-II	
	ACTUAL	PREDICTED	ACTUAL	PREDICTED
DONG 10a_opt.mds	8.1	7.92	6.3	6.46
DONG 10b_opt.mds	8.2	8.41	5.2	5.56
DONG 10c_opt.mds	7.7	8.17	6	6.09
DONG 10d_opt.mds	6.1	6.09	0	a
DONG 10e_opt.mds	8.5	8.44	7.7	7.88
DONG 10f_opt.mds	8.2	8.17	5.5	5.39
DONG 10g_opt.mds	8.8	8.57	a	a
DONG 10h_opt.mds	8	8.47	a	a
DONG 13a_opt.mds	7.6	8.08	6.5	6.67
DONG 13b_opt.mds	8.1	7.92	6.7	6.38
DONG 13c_opt.mds	8.3	8.23	6.6	6.69
DONG 13d_opt.mds	7.2	7.16	6.9	6.46
DONG 13e_opt.mds	7.5	7.61	6	5.27
DONG 18a_opt.mds	8.7	8.23	5	5.28
DONG 18b_opt.mds	8.3	8.47	a	a
DONG 18c_opt.mds	8.8	8.43	a	a
DONG 18d_opt.mds	8.5	8.57	a	a
DONG 18e_opt.mds	9	8.53	6.1	5.76
DONG 18f_opt.mds	7.6	7.98	6.9	6.8
DONG 18g_opt.mds	8.3	7.93	5.2	5.27
DONG 18h_opt.mds	8.7	8.51	4.8	5.56
DONG 18i_opt.mds	8.6	8.81	6.8	6.58

Figure-1 Graphical plot between actual and predicted activity values for DPP-II

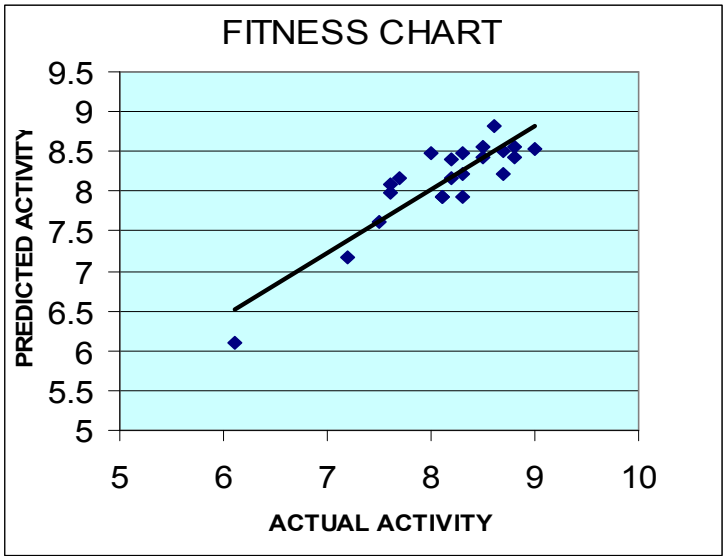


Figure-2 Graphical plot between actual and predicted activity values for DPP-IV

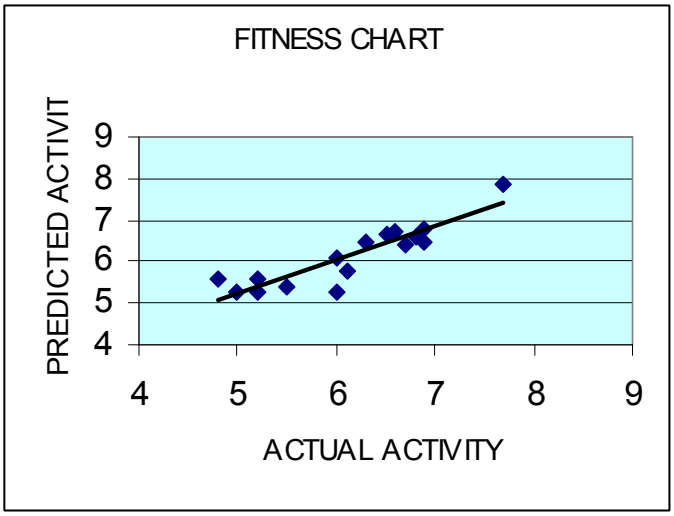


Figure-3 Contribution chart of the selected descriptors for DPP-II inhibition.

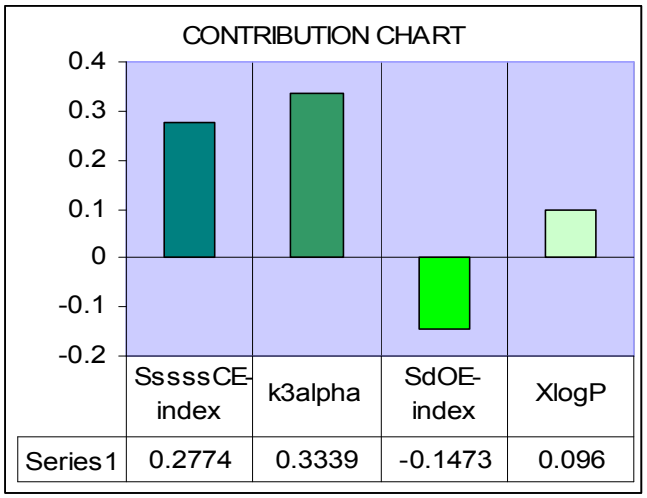
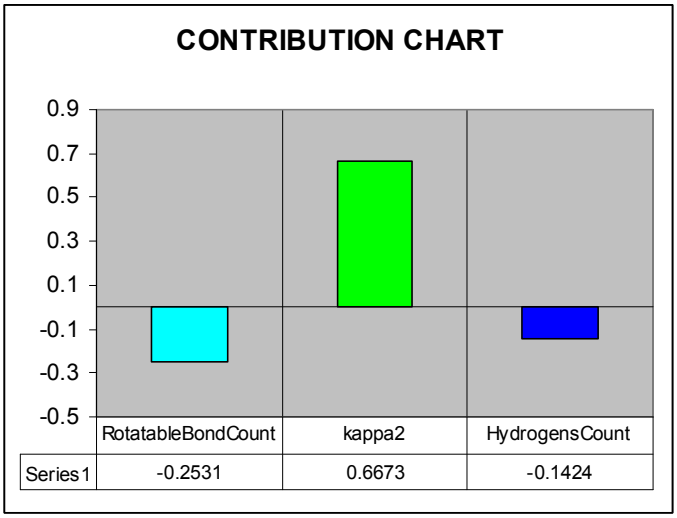


Figure-4 Contribution chart of the selected descriptors for DPP-IV inhibition.



Results And Discussion:

Although, generation of QSAR models with good statistical significance is of paramount importance, the models should also exhibit good predictive ability. The predictive ability of the models was gauged by a cross-validation procedure following a leave-one-out scheme. All the models exhibit high q2 and low r^2 se and q^2 se values confirm their excellent predictive potential. Furthermore, a comparison was made between the experimental activity values and predicted activity values calculated by using the obtained models in **Table 3** and graphical representations of the same are depicted in **Figures 1–2**. Graphical comparison shows a close agreement between actual and predicted values proves a good correlation. Where **a** is insignificant activity values of the compounds.After a profound study of model 1 and 2 for inhibitory activity toward DPP-IV and DPP-II, it was found that activity of compounds increases with increasing the number of carbon atoms connected to four single bonds, i.e. compound having tertiary butyl group are more active than others. Additional branching may hinder the binding of compounds to DPP-II enzymes active site. Thus by increasing carbon atom branching one may have better inhibition towards DPP-IV and a diminished inhibition towards DPP-II. As far as the electrotopology of the molecules is concerned, the compounds containing oxygen atoms connected to one double bond remarkably reduces DPP-IV inhibitory activity as exhibited by the compound **10d,** which has the lowest predicted activity among the whole set of compounds. In addition the above, inhibition of DPP-IV also depends on partition coefficient (XlogP) of the molecules. Positive correlation of this descriptor to the activity suggests that addition of groups which enhance partition coefficient may produce potent compounds against DPP-IV. Moreover molecular shape indices give positive contribution to both DPP-IV and DPP-II inhibitory activities. Contribution charts of the selected descriptors toward DPP-IV and DPP-II are given in figure 3 and 4 respectively.

Summarizing the above discussion, it may be concluded that a fair idea about drug–enzyme geometric fit can be achieved by using the descriptors SssssCE-index, k3alpha, SdOE-index, XlogP, RotatableBondCount, kappa2 and HydrogensCount. It can be clearly elucidated from the QSAR models that optimal DPP IV inhibitory activity may be achieved by incorporating hydrophobic groups and bulky groups especially at molecular terminals. Similarly for enhanced DPP II inhibition, the molecule should have structural rigidity and minimal hydrogen atoms

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