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Research Article

Identification of Some DPP-4 Inhibitors Using QSAR Modeling Based Drug Repurposing Approach

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Abstract

Post-prandial hyperglycemia still remains a problem in the management of type II diabetes mellitus. Of all available anti-diabetic drugs, DPP-4 inhibitors seem to be one of the most effective in reducing post-prandial hyperglycemia. In present study, QSAR modeling based drug repurposing approach has been implemented to identify some repurposed DPP-4 inhibitors with established safety profile. For this QSAR modeling based analysis, initially a (S)-1-((S)-2-amino-3-phenylpropanoyl) pyrrolidine-2-carbonitrile having two different types of substitutions i.e. R_1 on phenyl and R_2 on pyrrolidine as well as proper variation in the biological activity was selected thereafter models were developed using various conventional QSAR approaches including Free Wilson, Hansch, and Mixed modeling by utilizing PaDEL descriptor calculator and DTC lab software. Hansch type 2D QSAR model, which was derived using some PaDEL descriptor, showed acceptable internal as well as external consistencies. Some repurposed DPP-4 inhibitors were successfully identified. These identified approved drugs may be further explored as new anti-diabetics for type II diabetes patient especially for the management of post-prandial hyperglycemia which is a major issue in these patients

Keywords: QSAR, Hyperglycemia, Substitutions, Diabetes mellitus, PaDEL descriptor

1. INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia caused by inadequate insulin secretion with or without a simultaneous decrease in hormone action at its receptor [1].

Currently, diabetes is the fifth deadliest disease. As per WHO report, about 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades[2]. Post-prandial hyperglycemia still remains a problem in the management of type 2 diabetes mellitus. Of all available anti-diabetic drugs, Dipeptidyl peptidase - IV (DPP-4) inhibitors seem to be one of the most effective in reducing post-prandial hyperglycemia[3]. DPP- is a serine protease, which is present in membrane bound form and plasma soluble form[4]. The enzyme is responsible for degradation of number of biologically important peptides. DPP-IV deactivates GLP-1, so the DPP-IV inhibitors increase the activity of GLP-1. Inactivation of DPP-IV causes the increase in half-life of GLP-1**.** Most of the DPP-IV inhibitors are peptide derivatives of α-amino acyl pyrrolidines[5]. Currently numbers of DPP-IV inhibitors are available in the market due to high oral bioavailability like Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin and Omarigliptin [6]. Some of the FDA approved are displayed in **Fig. 1**

On the basis of these literature observations, it was thought worthwhile to identify some new α-glucosidase inhibitors with better safety profile therefore drug repurposing approach in combination with QSAR was considered to be better choice.

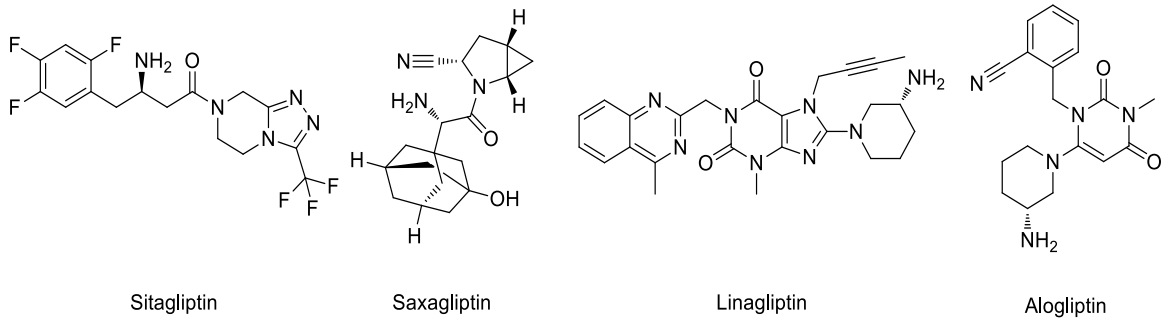


Figure 1: FDA approved DPP-4 inhibitors

Drug repurposing is gaining popularity as a quick and effective method of identifying new therapeutic indications of approved drugs unrelated to their original medical intent, and is successfully moving towards the second phase of clinical trials. In this study, drug repurposing with QSAR based virtual screening was implemented for identification of some DPP-4 inhibitors as new anti-diabetics. To carry of QSAR modeling against DPP-4 inhibitors, a congeneric series of (S)-1-((S)-2-amino-3-phenylpropanoyl) pyrrolidine-2-carbonitrile[7-9], as shown in **Fig. 2,** having two different types of substitutions i.e. R_1 on phenyl and R_2 on pyrrolidine as well as proper variation in the biological activity was selected on the basis the of thumb rules described by Hansch in his manual[10].

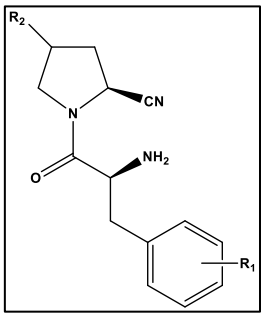


Figure 2: Basic scaffold of DPP-4 inhibitors used in QSAR modeling.

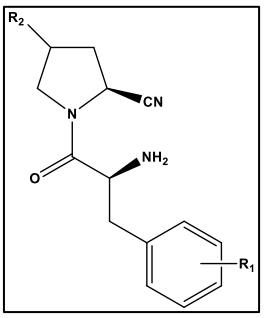
2. MATERIALS AND METHOD

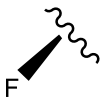
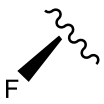
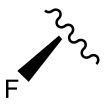
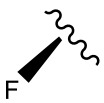
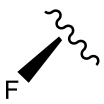
The study of DDP4 inhibitors was carried out using conventional various QSAR approaches including Free Wilson, Hansch, and Mixed modeling. For this purpose, various QSAR descriptors were collected from different sources like Hansch Manual, Medicinal chemistry books etc.[10, 11] and PaDEL software[12]. Indicator variables for deriving Free Wilson approach were formulated from the various substituents present on the parent scaffold. Hansch models were developed using substituent's constants collected from Hansch manual[10] and global properties of the inhibitors, which were calculated from the PaDEL software. QSAR models were derived by DTC QSAR modeling tool[13]. Internal and external validations were carried out by calculating various statistical parameters like Q^2, R^2_{traing}, R^2 test, PRESS, F values etc.

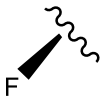
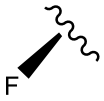
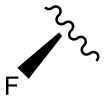
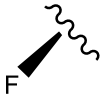
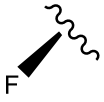
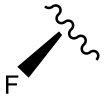
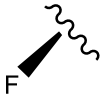
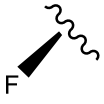
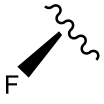
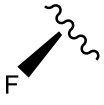
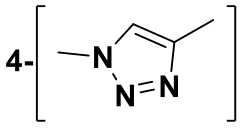
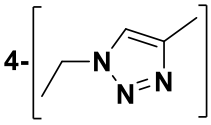
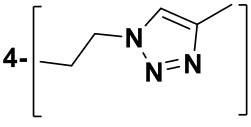
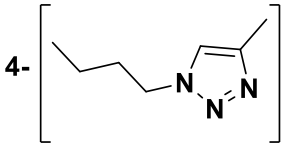
3 RESULTS AND DISCUSSION

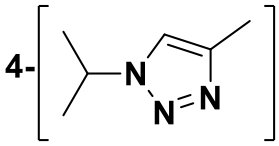
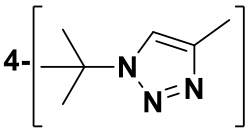
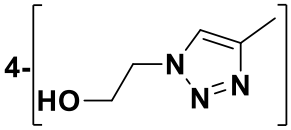
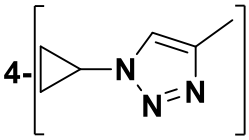
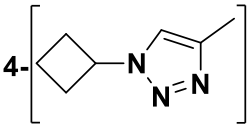
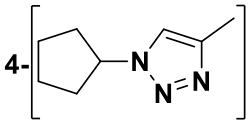
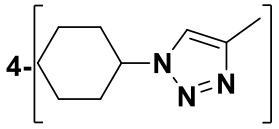
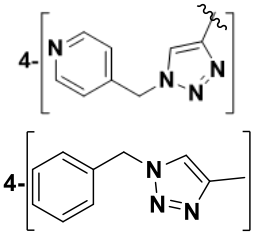
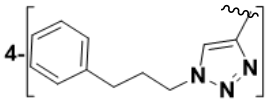
For QSAR modeling, a data set of DPP-4 inhibitors[7-9], was selected on the basis of thumb rules described by Hansch in his manual[10]. Data set containing 60 molecules was divided into training set of 45 molecules and test set of 15 molecules. Details about training set and test set are given in the **Table 1.** Training set was used for determining internal predictive ability whereas test set was used for external predictive ability of the QSAR model. Inhibitory activity data i.e. IC_{50} was collected from the literature. Here IC_{50} of the compounds represent their doses in nanomolar concentration required to produce 50% inhibition of DPP-4 enzyme. The given IC_{50} data is first converted into pIC_{50} by taking negative log of IC_{50}, where IC_{50} is in molar concentration. The values of pIC_{50} of all molecules in the data set are described in **Table 1**.

Table 1: Training set and test set data for QSAR analysis of DDP4 inhibitors



Compound	R1	R2	IC_{50}[a]	pIC_{50}[b]
1*	H	H	0.027	10.57
2	2-F	H	0.018	10.74
3	3-F	H	0.248	9.61
4	4-F	H	0.011	10.96
5	4-Me	H	0.017	10.77
6*	4-OMe	H	0.029	10.54
7	4-NH_2	H	0.075	10.12
8	4-NO_2	H	0.02	10.7
9	4-CN	H	0.021	10.68
10	4-CF_3	H	0.031	10.51
11	4-Cl	H	0.004	11.4
12	4-Br	H	0.004	11.4
13	4-Ph	H	0.145	9.84
14*	2-Me	H	0.042	10.38
15	2-CN	H	0.027	10.57
16	2-CF_3	H	0.046	10.34
17*	3-CN	H	0.063	10.2
18	3-CF_3	H	0.209	9.68
19*	H		0.017	10.77
20	4-F		0.003	11.52
21*	4-Me		0.004	11.4
22	4-OMe		0.015	10.82
23*	4-NO_2		0.029	10.54

24*	4-CN		0.005	11.3
25	4-CF_3		0.006	11.22
26	4-*t*Bu		0.125	9.9
27	4-OBn		0.094	10.03
28	2-CN		0.022	10.66
29	2-CF_3		0.02	10.7
30	2,4-F_2		0.006	11.22
31	2,4,5-F_3		0.017	10.77
32	2,3,4-F_3		0.023	10.64
33	2,3,5-F_3		0.06	10.22
34		H	0.265	9.58
35		H	0.339	9.47
36		H	0.374	9.43
37*		H	0.331	9.48

38		H	0.527	9.28
39		H	0.578	9.24
40		H	0.478	9.32
41		H	0.247	9.61
42		H	0.342	9.47
43*		H	0.332	9.48
44		H	0.863	9.06
45		H	9.39	8.03
46*		H	25.5	7.59
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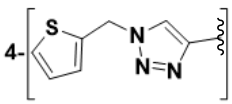
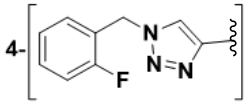
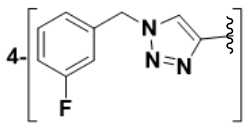
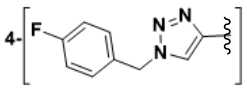
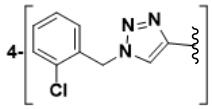
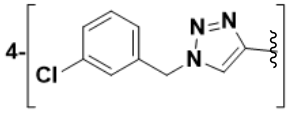
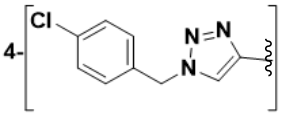
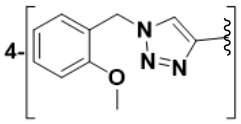
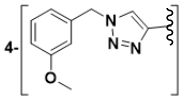
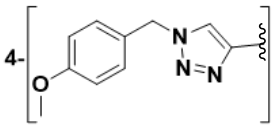
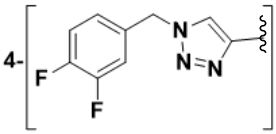
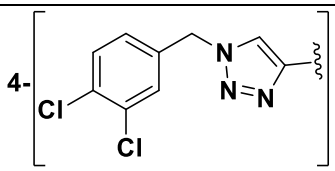
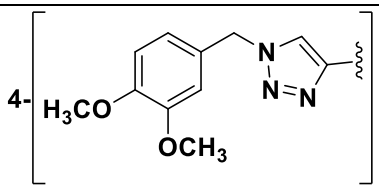
48		H	8.28	8.08
49		H	19.54	7.71
50*		H	7.56	8.12

51		H	3.79	8.42
52		H	15.24	7.82
53		H	10.45	7.98
54*		H	6.05	8.22
55		H	20.84	7.68
56		H	7.5	8.12
57		H	4.35	8.36
58*		H	8.57	8.07
59		H	10.02	8
60		H	15.7	7.8

* Test set compounds, [a]Dose in nanomolar concentration required to produce 50% inhibition of DPP-4, [b] –log IC_{50}

Total number of compounds: 60

Number of trainings:45, number of tests: 15

3.1 QSAR Model Development

QSAR modeling was started with Free Wilson approach. For this purpose various indicator variables were recorded for different functionality at R_1 by assigning value 1 for presence of the particular group and value 0 for absence of that group. Various Free Wilson models were developed taking pIC_{50} as dependent variable and various combination of indicator variables of R_1 as independent variables using multiple linear regression analysis. No model was found to be significant for predicting activity accurately. Thereafter, study was followed to develop Hansch QSAR models using some

local properties of the R_1 substituents. For this purpose stepwise multiple linear regression analysis was performed by considering pC_{50} as dependent variables and various substituent's constants which were collected from Hansch manual and Burger's Medicinal chemistry[10,11], as independent variables. In this analysis also, no models was found to be significant. Study was further subjected to Hansch type QSAR analysis by regression analysis using global proprieties of the inhibitors which were calculated by PaDEL software. The best model generated in this attempt is given in **Equation 1.** Correlation matrix of best model equation is given in **Table 2** to determine mutual correlation among the parameters present in this equation. These are free from mutual correlation. Values of Dependent (pIC_{50}) and independent variables (Descriptors) which were utilized in deriving **Equation 5.1** are given in **Table 5.3.**

pIC50 = 14.84288(+/-0.28854) -0.10092(+/-0.00655) *apol* -0.20639(+/-0.05306) *ATSC8p* +0.48633(+/-0.14694) *nssO* +0.06997(+/-0.02333) *VE3_D* ……**1**

Descriptions about selected variables are as follows:

***apol*(PaDEL; 2D)**=> 'Negative Contribution' =>Sum of the atomic polarizabilities (including implicit hydrogens)

***ATSC8p*(Dragon; 2D autocorrelations)**=> 'Negative Contribution' =>Centred Broto-Moreau autocorrelation of lag 8 weighted by polarizability

***nssO*(PaDEL; 2D)**=> 'Positive Contribution' =>Count of atom-type E-State: -O-

***VE3_D*(Dragon; 2D matrix-based descriptors)**=> 'Positive Contribution' =>logarithmic coefficient sums of the last eigenvector from topological distance matrix

Internal Validation Parameters:

SEE :0.34922, **r^2** :0.91955, **r^2 adjusted** :0.91151, **PRESS** :4.87812, **F** :114.30494 (**DF** :4, 40)

Leave-One-Out(LOO) Result :

Q2 :0.90415

Rm^2 metrics (after scaling the data):

Average rm^2(LOO):0.86499, **Delta rm^2(LOO):**0.06214

External Validation Parameters(Without Scaling):

r^2 :0.92569, **r0^2** :0.92332, **reverse r0^2**:0.9083, **RMSEP**:0.36579, **Q2f1/R^2(Pred)** :0.92043, **Q2f2** :0.92001

External Validation Parameters (After Scaling):

Average rm^2(test) :0.82937

Delta rm^2(test) :0.06883

Error based judgments of test set predictions:

Mean Absolute Error (MAE; 95% data): 0.28167

Standard Deviation of Absolute Error (SD; 95% data): 0.13951

Model Quality based on MAE-based criteria: 'GOOD'

Golbraikh and Tropsha acceptable model criteria's (7) :

****

1. **Q^2** 0.90415 **Passed** (Threshold value Q^2>0.5)

2. **r^2** 0.92569 **Passed** (Threshold value r^2>0.6)

3. **|r0^2-r'0^2|** 0.01501 **Passed** (Threshold value |r0^2-r'0^2|<0.3)

4. **k** 0.99239 [(r^2-r0^2)/r^2] 0.00256 OR*

k' 1.0063 [(r^2-r'0^2)/r^2] 0.01878 **Passed** (Threshold value: [0.85<k<1.15 and ((r^2-r0^2)/r^2)<0.1] OR* [0.85<k'<1.15 and ((r^2-r'0^2)/r^2)<0.1])

Table 2: Correlation matrix for the best QSAR model Equation **5.1**

	apol	ATSC8p	nssO	VE3_D
apol	1.000			
ATSC8p	-0.1334	1.000		
nssO	0.3206	0.2770	1.000	
VE3_D	-0.5889	-01256	-0.2826	1.000

Table 3: QSAR Descriptors of DPP-4 inhibitors

Name	pIC_{50}	apol	ATSC8p	nssO	VE3_D
2	10.74	39.96769	-1.76855	0	-6.00711
3	9.61	39.96769	-1.85127	0	-5.05077
4	10.96	39.96769	-1.59695	0	-4.27629
5	10.77	43.17107	-3.04585	0	-4.27629
7	10.12	41.84427	-2.30391	0	-4.27629
8	10.7	42.11469	-2.3054	0	-4.63571
9	10.68	42.27069	-3.15359	0	-4.13924
10	10.51	42.84169	-3.04369	0	-5.7751
11	11.4	41.59069	-3.93977	0	-4.27629
12	11.4	42.46069	-5.3656	0	-4.27629
13	9.84	53.30465	-3.25712	0	-6.16482
15	10.57	42.27069	-1.68551	0	-7.95386
16	10.34	42.84169	-3.04436	0	-6.23449
18	9.68	42.84169	1.326809	0	-10.7791
20	11.52	39.85789	-1.707	0	-4.0548
22	10.82	43.86327	-1.48249	1	-3.94653
25	11.22	42.73189	-3.15395	0	-5.2645
26	9.9	52.34203	-1.55704	0	-5.2645
27	10.03	57.09045	-1.96379	1	-4.66624
28	10.66	42.16089	-1.7747	0	-6.50901
29	10.7	42.73189	-3.13558	0	-7.88199
30	11.22	39.7481	-1.7376	0	-5.61252
31	10.77	39.63831	-1.85004	0	-8.02489
32	10.64	39.63831	-1.85004	0	-8.50818
33	10.22	39.63831	-2.10229	0	-15.2955
34	9.58	50.65786	-2.02214	0	-6.25004
35	9.47	53.75145	-2.63328	0	-6.35282
36	9.43	56.84503	-3.83216	0	-6.13481
38	9.28	56.84503	-3.26119	0	-7.20549
39	9.24	59.93862	-3.90149	0	-9.30993
40	9.32	54.55345	-3.07147	0	-6.13481

41	9.61	55.51145	-3.10086	0	-7.23285
42	9.47	58.60503	-3.95397	0	-7.64249
44	9.06	64.7922	-4.55289	0	-9.8782
45	8.03	63.88503	-2.52144	0	-7.93614
48	8.08	61.93145	-2.6132	0	-7.52736
49	7.71	63.77524	-2.61461	0	-10.5495
51	8.42	63.77524	-2.49978	0	-8.0663
52	7.82	65.39824	-1.2517	0	-10.5495
53	7.98	65.39824	-2.00415	0	-9.11949
55	7.68	67.78062	-1.98304	1	-14.7656
56	8.12	67.78062	-2.97056	1	-9.87002
57	8.36	67.78062	-0.74157	1	-7.90727
59	8	66.91145	-2.38925	0	-10.0602
60	7.8	71.6762	-1.23532	2	-14.3555
1*	10.57	40.07748	-1.74242	0	-4.17759
6*	10.54	43.97307	-1.36641	1	-4.13924
14*	10.38	43.17107	-2.7733	0	-6.00711
17*	10.2	42.27069	-0.7191	0	-5.33592
19*	10.77	39.96769	-1.85127	0	-3.97136
21*	11.4	43.06127	-3.154	0	-4.0548
23*	10.54	42.00489	-2.41429	0	-4.36414
24*	11.3	42.16089	-3.25218	0	-3.94653
37*	9.48	59.93862	-3.36961	0	-5.76647
43*	9.48	61.69862	-4.76556	0	-9.0776
46*	7.59	66.97862	-1.56279	0	-6.88244
47*	7.75	62.55824	-2.79883	0	-7.93614
50*	8.12	63.77524	-2.55671	0	-9.11949
54*	8.22	65.39824	-2.87984	0	-8.0663
58*	8.07	63.66545	-2.53519	0	-10.0602

Statistical evaluation of **Equation 1** clearly demonstrated that model is having acceptable values of primary statistical parameters including SEE: 0. 0.34922, r^2 : 0.91955, r^2 adjusted : 0.91151, PRESS : 4.87812, F : 114.30494, Q^2 : 0.90415 which determine internal consistency of the best model, **Equation 1,** and **r^2** : 0.92569, r_0^2 : 0.92332, reverse r_0^2 : 0.9083, RMSEP: 0.36579, Q^2f1 or R2(Pred) : 0.92043, Q2f2 : 0.92001 Average rm^2(test) : 0.82937, Delta rm^2(test) : 0.06883 which determine external predictive ability of the best model. Other criterion including Model Quality based on MAE-based criteria and Golbraikh and Tropsha acceptable model criteria's[also pass the model for its acceptability to use it for designing of new DPP-4 inhibitors and prediction their activities. Predicted activities of training and test set molecules from the best model, **Equation 1**, along with residual values are given in **Table 4.** Graph of observed vs predicted activities from the best model of the training and test set molecules is shown in **Fig. 3** and compound vs residual is shown in **Fig. 4.** These graphs clearly indicate that most of the compounds predicted within ± 0.5 pIC_{50} units.

Table 4: Predicted activities of training and test set molecules along with residual values

NAME	OBS pIC_{50}[a]	PRED. pIC_{50}[b]	RESIDUAL
4	10.960	10.778	0.033
6	10.540	10.789	0.062
7	10.120	10.502	0.146
8	10.700	10.540	0.026
10	10.510	10.748	0.057
11	11.400	10.769	0.398
12	11.400	10.766	0.402
16	10.340	10.748	0.166
17	10.200	10.845	0.416
18	9.680	10.748	1.140
20	11.520	10.770	0.562
21	11.400	10.761	0.408
22	10.820	10.780	0.002
23	10.540	10.528	0.000
25	11.220	10.741	0.230
26	9.900	10.717	0.668
27	10.030	9.357	0.453
29	10.700	10.741	0.002
30	11.220	10.761	0.211
31	10.770	10.752	0.000
32	10.640	10.752	0.013
33	10.220	10.752	0.283
34	9.580	9.440	0.020
35	9.470	9.426	0.002
36	9.430	9.414	0.000
38	9.280	9.413	0.018
39	9.240	9.395	0.024
40	9.320	9.110	0.044
41	9.610	9.432	0.032
45	8.030	8.015	0.000
46	7.590	8.005	0.172
47	7.750	8.044	0.087
48	8.080	8.085	0.000
49	7.710	8.008	0.089
50	8.120	8.008	0.013
51	8.420	8.008	0.170
52	7.820	8.002	0.033
53	7.980	8.002	0.001

54	8.220	8.002	0.047
55	7.680	8.016	0.113
56	8.120	8.016	0.011
57	8.360	8.016	0.119
58	8.070	8.001	0.005
59	8.000	7.992	0.000
60	7.800	8.017	0.047
1*	10.570	10.789	0.048
2*	10.740	10.778	0.001
3*	9.610	10.778	1.365
5*	10.770	10.769	0.000
9*	10.680	10.845	0.027
13*	9.840	9.355	0.236
14*	10.380	10.769	0.151
15*	10.570	10.845	0.076
19*	10.770	10.779	0.000
24*	11.300	10.835	0.217
28*	10.660	10.835	0.031
37*	9.480	9.402	0.006
42*	9.470	9.419	0.003
43*	9.480	9.407	0.005
44*	9.060	9.396	0.113

* Test compounds, [a] - $\log IC_{50}$, where IC_{50} is experimental reported in the literature,

[b] predicted $-\log(IC_{50})$ from the best model **Equation 5.1**

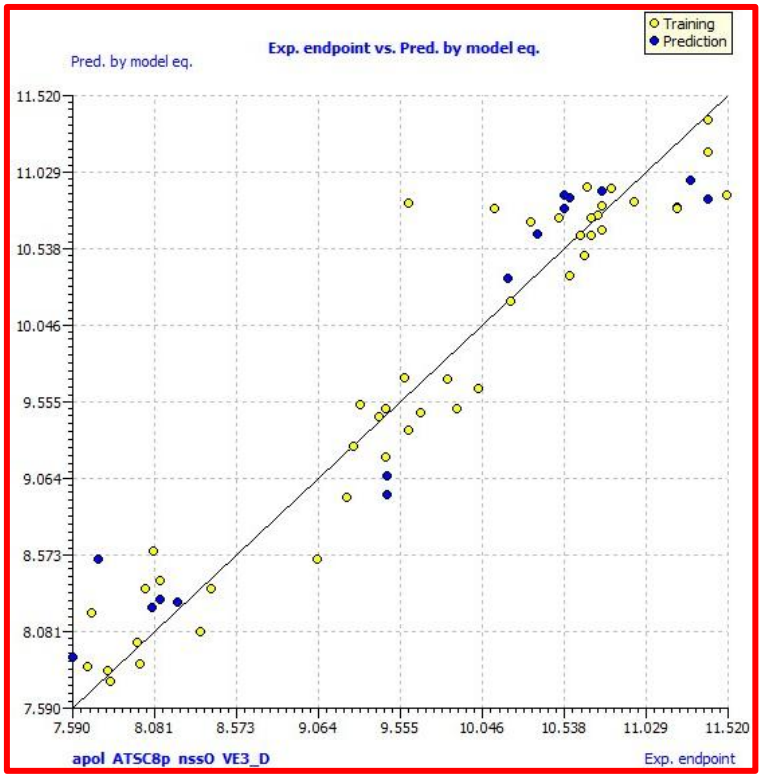


Figure 3: Graph of observed vs predicted activity from the best model **Equation 1**.

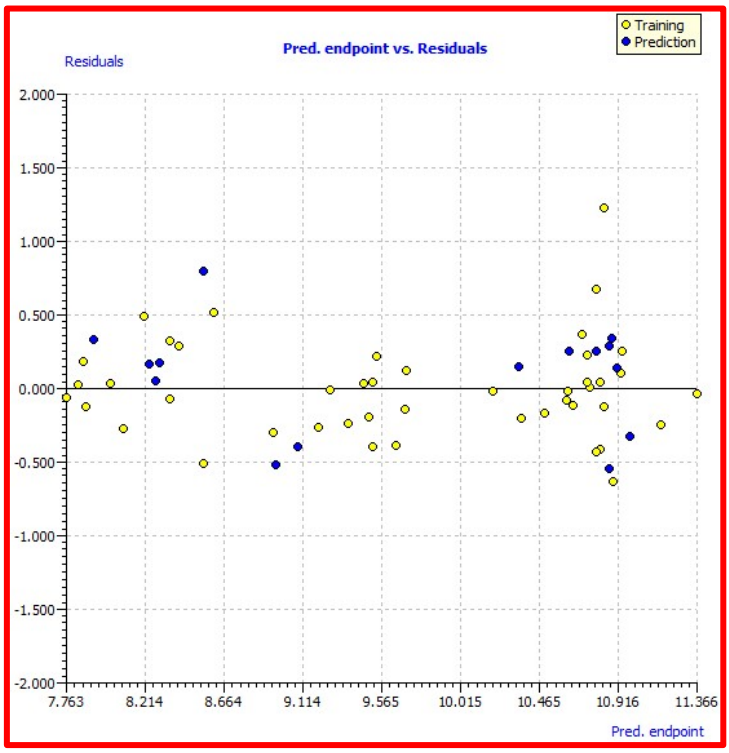


Figure 4: Resisual plot for training and test set

Some DPP-4 inhibitors were identified by QSAR model based virtual screening (VS) protocol. VS is a computational technique used in identification new bioactive molecules. It deals with the quick search of large libraries of chemical structures in order to identify those structures which are most likely to map over the query *in silico* model. For this purpose, the best QSAR model of DPP-4 inhibitors, given in **Equation 1,** was used to screen out some α-glucosidase inhibitors as NCE with anti-diabetic effect. These best models were used as filters for screening DRUGBANK using Predict Module of DTC QSAR tool[13, 14]. To predict activities of the screened out molecules, descriptors of these were calculated by PaDEL software[12]. Some identified DPP-4 inhibitors along with predicted pIC_{50} from **Equation1** is given in **Table 5**. Top ten repurposed DPP-4 inhibitors screened out by virtual screening using **Equation 1** as query against DRUGBANK are shown in **Fig.5.**

Table 5: Newly identify DPP-4 inhibitors as anti-diabetic drug

Name	Pred. pIC_{50}	AD status	Name
DB11359	13.230	Inside-AD	Guaiacol
DB14482	13.110	Inside-AD	Sodium ascorbate
DB00347	13.061	Inside-AD	Trimethadione
DB00356	13.053	Inside-AD	Chlorzoxazone
DB00545	13.017	Inside-AD	Pyridostigmine
DB13882	13.010	Inside-AD	Heat spray
DB09041	12.948	Inside-AD	5-fluoro-3h-2,1-benzoxaborol-1-ol
DB04564	12.882	Inside-AD	Gluconolactone
DB14212	12.832	Inside-AD	Paraben
DB11304	12.830	Inside-AD	Phenoxyethanol
DB09543	12.819	Inside-AD	Methyl salicylate
DB00617	12.765	Inside-AD	Paramethadione
DB13853	12.738	Inside-AD	Halpen
DB00122	12.726	Inside-AD	Choline

DB04173	12.715	Inside-AD	° -L-fructofuranose
DB00114	12.693	Inside-AD	Pyridoxal phosphate
DB04948	12.671	Inside-AD	Lofexidine
DB00888	12.663	Inside-AD	Mechlorethamine
DB08797	12.648	Inside-AD	Salicylamide
DB00331	12.643	Inside-AD	Metformin
DB01296	12.637	Inside-AD	Glucosamine
DB13982	12.632	Inside-AD	(177lu)lutetium
DB09220	12.619	Inside-AD	2-nicotinamidoethyl nitrate
DB00740	12.616	Inside-AD	Riluzole
DB00129	12.600	Inside-AD	Ornithine
DB00130	12.589	Inside-AD	L-glutamine
DB15793	12.588	Inside-AD	Unii-71th42o2cq
DB09210	12.580	Inside-AD	Fidaxomicin
DB13628	12.564	Inside-AD	Ethylparaben
DB00189	12.562	Inside-AD	Ethchlorvynol
DB00352	12.558	Inside-AD	Thioguanine
DB13076	12.552	Inside-AD	(90y)yttrium
DB00336	12.548	Inside-AD	Nitrofurazone
DB14188	12.54	Inside-AD	2-methoxy-4-propenylphenol
DB01164	12.541	Inside-AD	Calcium chloride
DB01086	12.540	Inside-AD	Benzocaine
DB09276	12.538	Inside-AD	Gold sodium thiomalate
DB00787	12.537	Inside-AD	Aciclovir
DB01004	12.531	Inside-AD	Gancyclovir
DB00733	12.527	Inside-AD	Pralidoximum
DB09086	12.521	Inside-AD	Eugenol
DB01018	12.519	Inside-AD	Guanfacine
DB00244	12.518	Inside-AD	Mesalazine
DB06151	12.512	Inside-AD	Acetylcysteine
DB00766	12.503	Inside-AD	Clavulanate
DB09269	12.500	Inside-AD	?-Phenylacetic acid
DB00389	12.486	Inside-AD	Carbimazole
DB02362	12.478	Inside-AD	Sunbrella
DB00859	12.472	Inside-AD	Depen
DB12091	12.471	Inside-AD	Gadolinium
DB00793	12.467	Inside-AD	Haloprogin
DB09153	12.461	Inside-AD	Sodium chloride
DB11151	12.461	Inside-AD	Sodium hydroxide
DB11159	12.461	Inside-AD	Disodium sulfanediide

DB01230	12.460	Inside-AD	Pemoline
DB11323	12.460	Inside-AD	Glycol salicylate
DB13269	12.457	Inside-AD	2,4-dichlorobenzyl alcohol
DB01080	12.449	Inside-AD	Vigabatrin
DB14177	12.431	Inside-AD	Propylparaben
DB02893	12.424	Inside-AD	(L)-methionine
DB13972	12.424	Inside-AD	Methionine
DB14199	12.416	Inside-AD	Methyldibromo glutaronitrile
DB14193	12.411	Inside-AD	Lugol's iodine
DB00916	12.408	Inside-AD	Metronidazole
DB14184	12.405	Inside-AD	Cinnamal
DB00233	12.394	Inside-AD	Aminosalicylic acid
DB14506	12.390	Inside-AD	Lithium hydroxide
DB00513	12.386	Inside-AD	Aminocaproic acid
DB15916	12.386	Inside-AD	(1r,3s,4s)-3-bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one
DB09256	12.382	Inside-AD	Tegafur
DB09327	12.382	Inside-AD	Tegafur; uracil
DB14084	12.366	Inside-AD	Butylparaben
DB00593	12.352	Inside-AD	Ethosuximide
DB09473	12.342	Inside-AD	(111in)indium(3+) ion tris(quinolin-8-olate)
DB09242	12.333	Inside-AD	Moxonidine
DB11148	12.332	Inside-AD	Butamben
DB06243	12.320	Inside-AD	Vaniqa
DB09400	12.313	Inside-AD	Selenomethionine se 75
DB11142	12.313	Inside-AD	L-selenomethionine
DB13218	12.287	Inside-AD	Mandelic acid
DB00879	12.286	Inside-AD	Emtricitabine
DB00316	12.282	Inside-AD	Acetaminophen
DB11145	12.274	Inside-AD	8 hydroxyquinoline
DB11121	12.274	Inside-AD	Dettol
DB00853	12.270	Inside-AD	N-demethyldiltiazem
DB11156	12.265	Inside-AD	Pyrantel
DB04339	12.264	Inside-AD	Carbocisteine
DB00709	12.263	Inside-AD	Lamivudine
DB01031	12.262	Inside-AD	Ethinamate
DB05018	12.256	Inside-AD	Migalastat
DB00856	12.251	Inside-AD	Chlorphenesin
DB00811	12.249	Inside-AD	Ribavirin
DB06698	12.229	Inside-AD	Betahistine
DB00262	12.224	Inside-AD	Carmustine

DB14186	12.211	Inside-AD	Cinnamyl alcohol
DB00780	12.199	Inside-AD	Phenelzine
DB06775	12.182	Inside-AD	Carglumic acid
DB00123	12.173	Inside-AD	Unii-71th42o2cq
DB11496	12.168	Inside-AD	2(3h)-benzothiazolethione
DB01143	12.164	Inside-AD	Amifostine
DB00659	12.157	Inside-AD	Acamprosate
DB00594	12.156	Inside-AD	Pentostatin

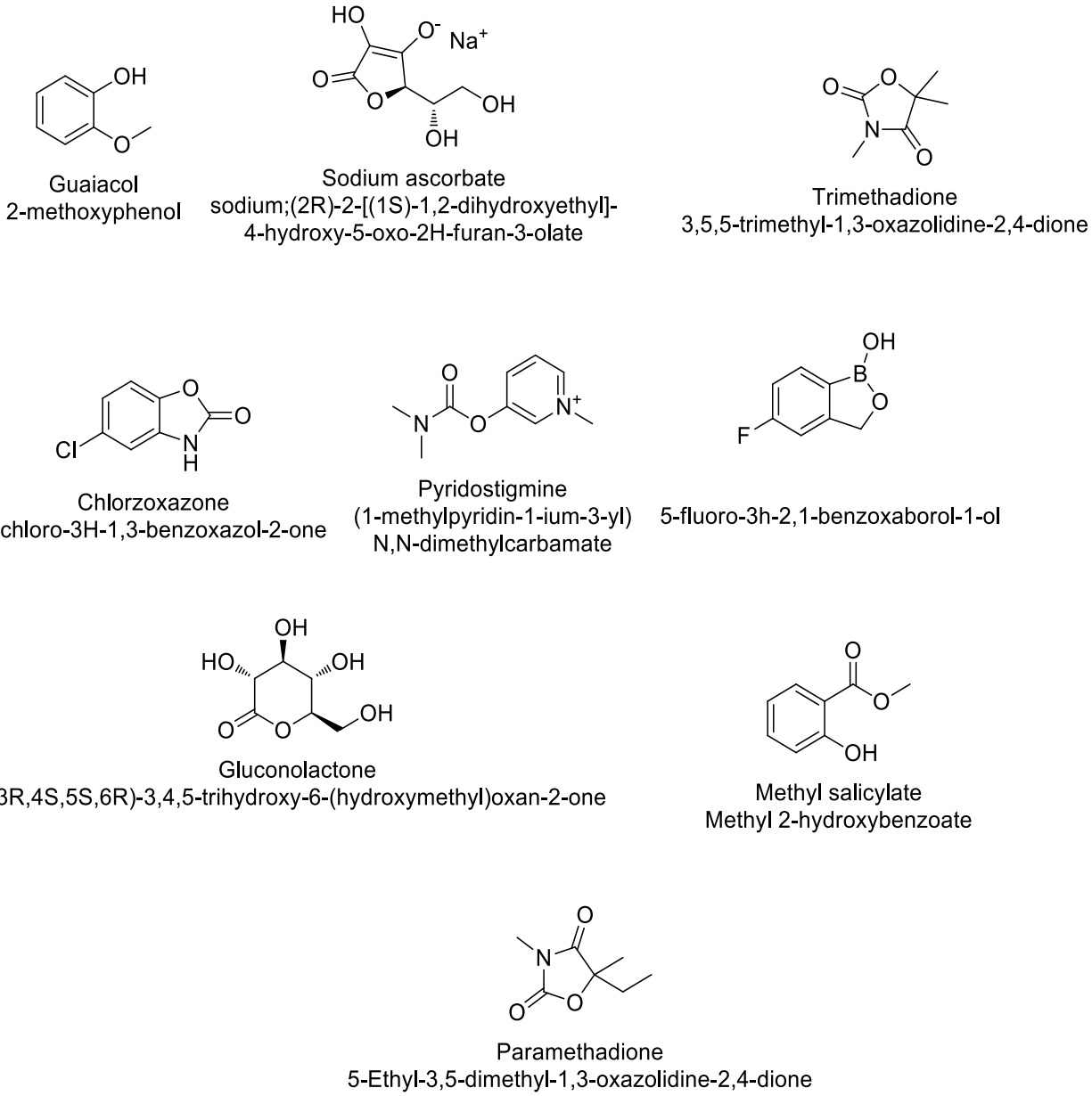


Figure 5: Top ten repurposed DPP-4 inhibitors screened out by virtual screening using **Equation 1** as query against DRUGBANK.

4. CONCLUSION

On the basis of this QSAR modeling of DDP-4 inhibitory activity, it can concluded that a Hansch type two dimensional QSAR model has been successfully developed by utilizing some PaDEL descriptors for a set of (S)-1-((S)-2-amino-3-phenylpropanoyl) pyrrolidine-2-carbonitrile derivatives. Generated model was thoroughly evaluated by means of all reported statistical parameters. This validation results of the best model **Equation 1** are in acceptable criterion and therefore suggest model's reliability to be used in VS for identifying repurposed DPP-4 inhibitors which may be further develop as new effective anti-diabetic in management of post-prandial hyperglycemia in the type II diabetes without additional safety measurement.

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