WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 777-788. Research Article ISSN 2277– 7105

2D QSAR MODEL BASED ON PYRIDINECARBOXAMIDE AND BENZAMIDE DERIVATIVES AS GLUCOKINASE ACTIVATOR

Dhanraj Patidar[1]*, Ashish Jain[2] and Pradeep Kumar Mohanty[2]

[1]Radharaman College of Pharmacy, Ratibad, Bhopal 462046.

[2]School of Pharmacy, LNCT University, Kolar, Road Bhopal, M.P., India.

Article Received on
29 June 2018,

Revised on 19 July 2018,
Accepted on 08 August 2018

DOI: 10.20959/wjpr201816-13103

***Corresponding Author**
Dhanraj Patidar
Radharaman College of Pharmacy, Ratibad, Bhopal 462046.

ABSTRACT

Background: 58 compounds were chosen from the published article having two basic moieties i.e. pyridinecarboxamide and benzamide derivatives. **Method:** Work station was a computer with operating system and mass storage facility integrated with graphical display. All the computational studies were performed on a Microsoft Window XP running on Pentium-D- processor. QSAR study has been done by using the Vlife MDS software provided by Vlife Sciences Technologies Pvt. Ltd. Pune, India. **Results:** From this plot it has been seen that model is able to predict the activity of the training set quite well (all points are close to regression line) as well as external test set (all points of test set are close to regression line and well covered by training points), providing confidence in predictive ability of the model. **Conclusion:** Statistic of model DP1 reveals correlation coefficient (r^2 = 0.9017), internal predictive ability (q^2 = 0.8617) and external predictive ability for the test molecules (Pred r^2 = 0.8138). The low standard error i.e. r^2 se = 0.24, q^2 se = 0.29 and Pred r^2se = 0.28 demonstrates accuracy of the model. Values of different statistical parameters of model DP1 are within the limit for providing the best fit.

KEYWORDS: Quantitative structure activity relationship, Diabetes mellitus, Glucokinase enzyme, Glucokinase activator, Optimization.

INTRODUCTION

QSAR is a widely used technique in drug design process. It employs statistics and analytical tools to investigate the relationship between the structures of ligands and their corresponding effects. Hence, mathematical models are built based on structural parameters to describe the structure activity relationship.[1,3]

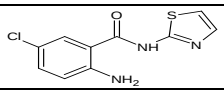
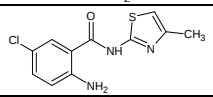
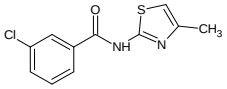
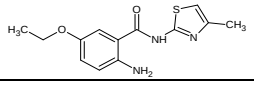
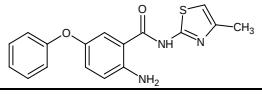
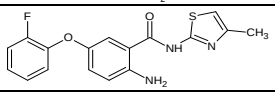
Diabetes mellitus is a group of metabolic disorder in which a person has high blood sugar level due to dysregulation of glucose metabolism, β-cell dysfunction and impaired insulin sensitivity. There are mainly three types of diabetes:- Type 1 diabetes, Type 2 diabetes and Gestational diabetes.[4,8]

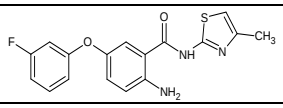
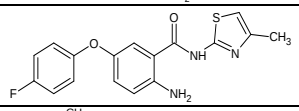
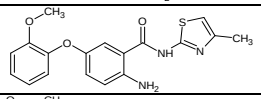
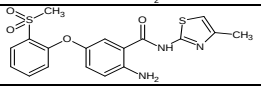
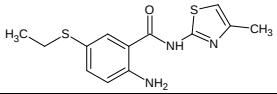
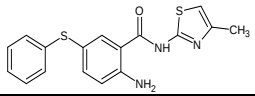
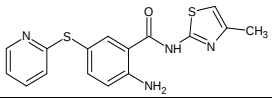
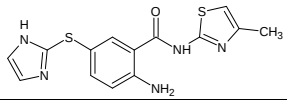
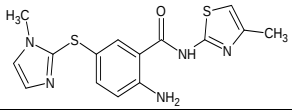
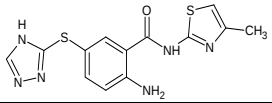
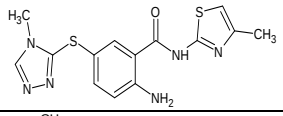
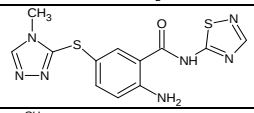
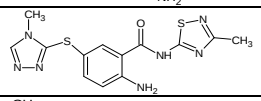
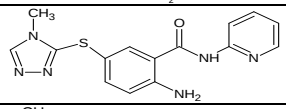
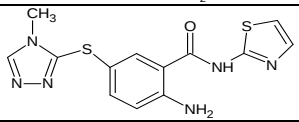
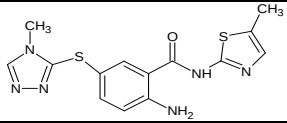
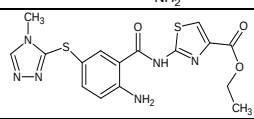
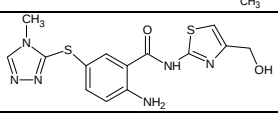
Glucokinase (GK) is an enzyme of the hexokinase family that catalyzes the first step in glycolysis. *Glucokinase* occurs in cells in the liver, pancreas, gut and brain of humans and most other vertebrates and causes phosphorylation of glucose to glucose 6-phosphate. It plays a significant role as a glucose sensor to maintain the plasma glucose level by enhancing both glucose uptake in the liver and insulin secretion from pancreatic β-cells. There is still a significant medical need for novel agents that modulate glucose levels with greater and longer lasting efficacy. Results from several recent studies including emerging clinical data have demonstrated that small-molecule *glucokinase* activators may be able to fill this void.[9,12]

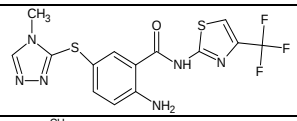
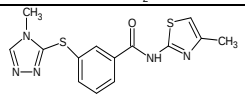
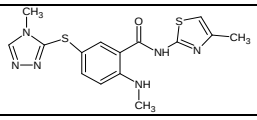
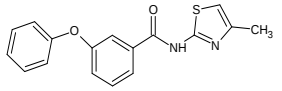
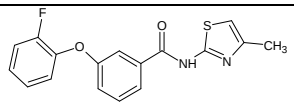
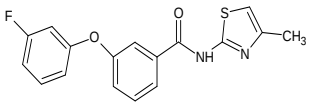
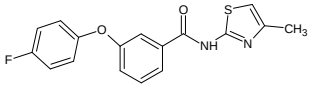
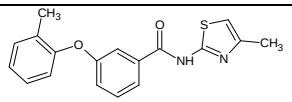
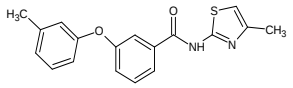
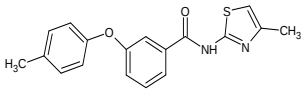
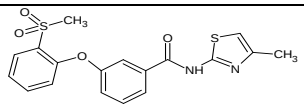
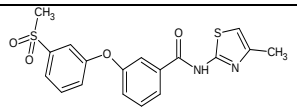
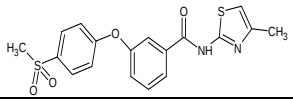
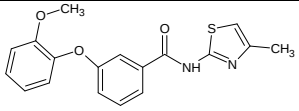
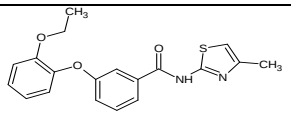
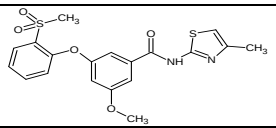
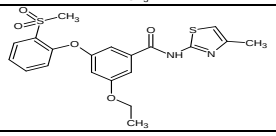
MATERIAL AND METHOD

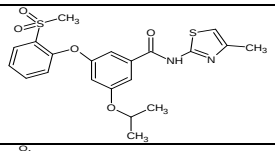
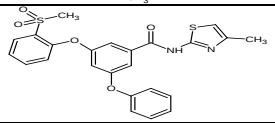
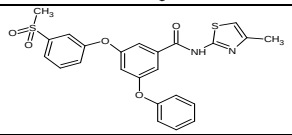
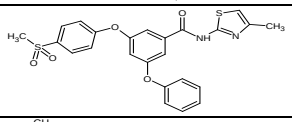
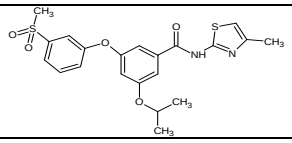
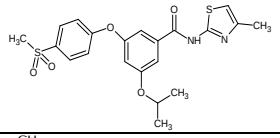
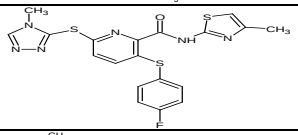
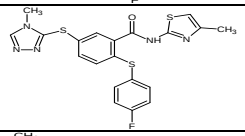
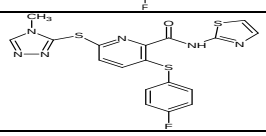
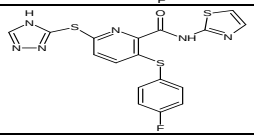
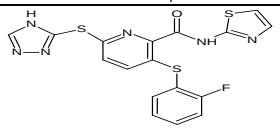
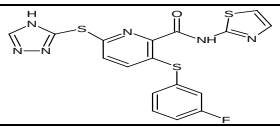
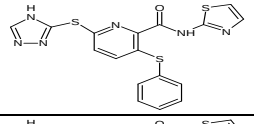
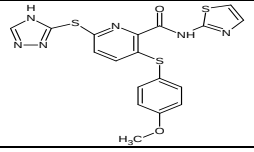
Work station was a computer with operating system and mass storage facility integrated with graphical display. All the computational studies were performed on a Microsoft Window XP running on Pentium-D-processor. QSAR study has been done by using the Vlife MDS software provided by Vlife Sciences Technologies Pvt. Ltd. Pune, India. 58 compounds were chosen from the published article having two basic moieties i.e. pyridinecarboxamide and benzamide derivatives.[13,15]

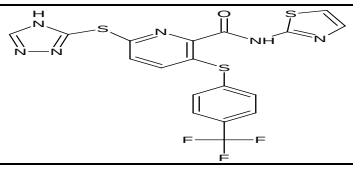
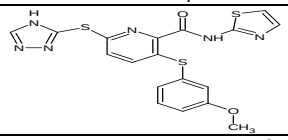
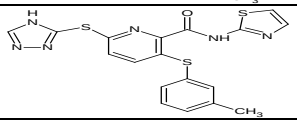
Table 1: List of Compounds used for the QSAR Studies of *Glucokinase* Activator.

Code	Structure	EC_{50}(μM)	pEC_{50}
DR01		11	-1.0413
DR02		6.5	-0.8129
DR03		17	-1.2304
DR04		6.8	-0.8325
DR05		0.70	0.1549
DR06		0.26	0.5850

DR07		0.60	0.2218
DR08		1.7	-0.2304
DR09		0.41	0.3872
DR10		0.51	0.2924
DR11		0.78	0.1079
DR12		0.92	0.0362
DR13		1.2	-0.0791
DR14		1.6	-0.2041
DR15		0.23	0.6382
DR16		2.4	-0.3802
DR17		0.42	0.3767
DR18		0.49	0.3098
DR19		0.64	0.1938
DR20		1.2	-0.0791
DR21		0.35	0.4559
DR22		0.33	0.4814
DR23		1.1	-0.0413
DR24		1.6	-0.2041

DR25		2.7	-0.4313
DR26		7.3	-0.8633
DR27		1.1	-0.0413
DR28		19	-1.2787
DR29		2.4	-0.3802
DR30		6.3	-0.7993
DR31		21	-1.3222
DR32		3.2	-0.5051
DR33		8.2	-0.9138
DR34		5.9	-0.7708
DR35		5.5	-0.7403
DR36		18	-1.2552
DR37		29	-1.4623
DR38		2.2	-0.3424
DR39		5.4	0.7323
DR40		11	-1.0413
DR41		2.4	-0.3802

DR42		2.1	-0.3222
DR43		1.1	-0.0413
DR44		1.1	-0.0413
DR45		0.42	0.3767
DR46		1.1	-0.0413
DR47		0.33	0.4814
DR48		0.25	0.6010
DR49		0.97	0.0132
DR50		0.12	0.9208
DR51		0.07	1.1191
DR52		0.05	1.2441
DR53		0.04	1.3979
DR54		0.03	1.4202
DR55		0.12	0.9208

DR56		0.16	0.7958
DR57		0.16	0.7958
DR58		0.10	1.0000

Structure Draw: Structures were drawn in 2D by Chem Sketch and these 2D structures were converted into 3D and saved in .mol2 file format.

Optimization of 3D Structure: The 3D structures were optimized in batch optimization by using merck molecular force field (MMFF) method. Number of cycle 100000 was input for achieving global minimization energy at the converse of 0.01.

2D QSAR: Descriptor sheet of 2D QSAR was prepared by inserting the optimized compounds and biological activity and selecting the physicochemical, alignment independent and topological descriptors (structural descriptors). Total 9352 descriptors were obtained but after removing invariable column 495 descriptors were left.

For the generation of 2D QSAR model, the test and training set were selected by using manual data selection method. The regression was done by partial least square analysis (PLS). Further processing of the statistical method was done by using forward-backward method. Setting value as cross correlation limit: 0.5, F-in: 4.00, F-out: 3.99, number of variable in final equation: 495, variance cut off: 0.0, scaling: auto scaling, various 2D models were generated.

2D QSAR Models

Table 2: Descriptor Sheet of 2D QSAR.

Code	A	B	C	D	E	F	G
DR01	3	0	0	0	0	0	0
DR02	3	0	0	0	0	0	0
DR03	1	0	0	0	0	0	0
DR04	5	0	0	0	0	0	0
DR05	7	0	0	0	0	0	0
DR06	7	0	0	0	0	2	0
DR07	7	0	0	0	0	0	0

DR08	7	0	0	0	1	0	0
DR09	7	0	0	0	0	0	1
DR10	7	0	0	0	0	0	0
DR11	5	0	0	0	0	0	0
DR12	7	0	0	0	0	0	0
DR13	5	0	0	0	0	0	0
DR14	3	1	0	0	0	0	0
DR15	3	0	0	2.059327	0	0	0
DR16	5	1	0	0	1	0	0
DR17	5	0	0	1.948216	1	0	0
DR18	6	0	0	1.937197	0	0	0
DR19	6	0	0	1.939952	1	0	0
DR20	5	0	0	1.931943	1	0	0
DR21	5	0	0	1.945461	0	0	0
DR22	5	0	0	1.948216	1	0	0
DR23	6	0	0	1.91462	5	0	0
DR24	5	0	0	1.92802	3	0	0
DR25	5	0	0	1.846915	7	0	0
DR26	3	0	0	1.972663	1	0	0
DR27	6	0	0	1.971653	1	0	0
DR28	3	0	0	0	0	0	0
DR29	3	0	0	0	0	1	0
DR30	3	0	0	0	0	0	0
DR31	3	0	0	0	1	0	0
DR32	3	0	0	0	0	0	0
DR33	3	0	0	0	0	0	0
DR34	3	0	0	0	1	0	0
DR35	3	0	0	0	0	0	0
DR36	3	0	2	0	3	0	0
DR37	3	0	0	0	1	0	0
DR38	3	0	0	0	0	0	1
DR39	3	0	0	0	1	0	1
DR40	3	0	0	0	0	0	0
DR41	4	0	0	0	0	0	0
DR42	5	0	0	0	0	0	0
DR43	5	0	0	0	0	0	0
DR44	5	0	2	0	3	0	0
DR45	5	0	2	0	1	0	0
DR46	5	0	2	0	3	0	0
DR47	5	0	2	0	1	0	0
DR48	8	0	0	1.931516	4	1	0
DR49	6	0	0	1.971516	4	0	0
DR50	7	0	0	1.928761	3	1	0
DR51	7	1	0	0	3	1	0
DR52	7	1	0	0	1	0	0
DR52	7	1	0	0	2	1	0
DR54	7	1	0	0	1	0	0
DR55	7	1	0	0	4	0	0

DR56	7	1	0	0	6	0	0
DR57	7	1	0	0	4	0	0
DR58	8	1	0	0	2	0	0

Where **A:** T_C_N_7, **B:** SaaNHcount, **C:** T_O_O_10, **D:** SaasN(Noxide)E-index, **E:** T_T_N_12, **F:** T_N_F_8, **G:** T_O_O_3.

Table 3: Uni-Column Statistics of Model DP1.

	Column Name	Average	Max	Min	StdDev	Sum
Training	pEC_{50}	-0.0765	1.4202	-1.462	0.7495	-3.289
Test	pEC_{50}	0.0645	1.3979	-0.799	0.6409	0.7743

In model DP1 the max of training was higher than the test set where as in case of min the test set had high value than the training set. The standard deviation lies in between 0.64 to 0.74.

Values of Different Statistical Parameters of Model DP1

r^2 = 0.9017, r^2se = 0.2470, q^2 = 0.8617, q^2se = 0.2930, Pred r^2 = 0.8138, Pred r^2se = 0.2837, F-test = 87.1589, Optimum component = 4, Degree of freedom = 38, n = 43.

Equation of Model DP1

PEC50 = + 0.2639 T_C_N_7 + 1.1102 SaaNHcount + 0.3934 T_O_O_10 + 0.2691 SaasN(Noxide)E-index - 0.1184 T_T_N_12 + 0.3748 T_N_F_8 + 0.2863 T_O_O_3 -1.6927.

Table 4: Correlation Matrix of Model DP1.

	A	B	C	D	E	F	G
A	1	0.476	-0.113	-0.012	0.202	0.384	0.213
B	0.476	1	-0.110	-0.128	-0.265	0.271	0.102
C	-0.113	-0.110	1	-0.087	-0.180	-0.170	-0.087
D	-0.012	-0.128	-0.087	1	-0.210	0.120	-0.102
E	0.202	-0.265	-0.180	-0.210	1	0.389	0.136
F	0.384	0.271	-0.170	0.120	0.389	1	0.216
G	0.213	0.102	-0.087	-0.102	0.136	0.216	1

Where **A:** T_C_N_7, **B:** SaaNHcount, **C:** T_O_O_3, **D:** T_O_O_10, **E:** SaasN(Noxide)E-index, **F:** T_T_N_12, **G:** T_N_F_8.

The descriptor T_C_N_7 showed high contribution (47%) and lowest contribution (0.01%) with SaaNHcount and T_O_O_10 respectively.

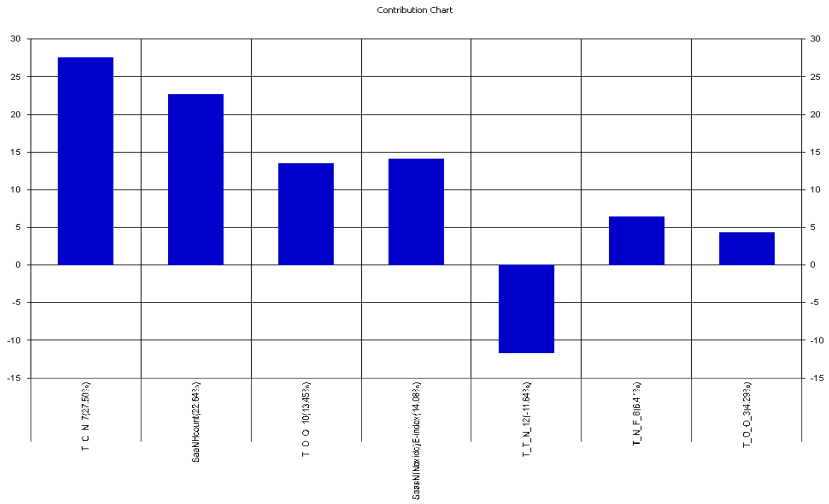


Chart 1: Contribution Chart of Model DP1.

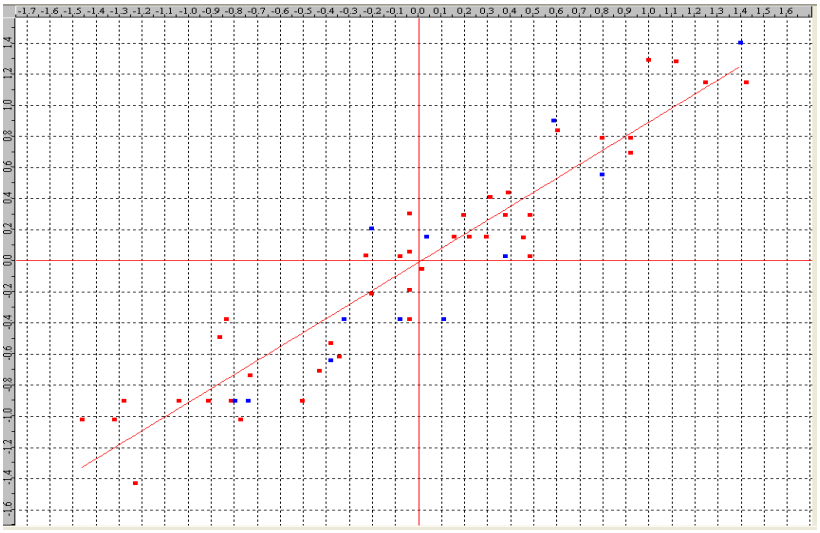
In this model seven descriptors, T_C_N_7, SaaNHcount, T_O_O_10, SaasN(Noxide)E-index, T_T_N_12, T_N_F_8 and T_O_O_3 were found to be highly correlated with biological activity. The descriptor T_C_N_7 showed high contribution (27.50%) in determining the antidiabetic activity. It suggests that increase in the T_C_N_7 will be favorable for the activity and T_T_N_12 showed negative contribution (-11.64%) is inversely proportional to the activity.

Table 5: Predicted Activity of Model DP1.

Code	Actual activity in $pEC_{50\ (\mu M)}$	Predicted activity	Residual
DR01	-1.0413	-0.90083	-0.14047
DR02	-0.8129	-0.90083	0.087931
DR03	-1.2304	-1.42872	0.198317
DR04	-0.8325	-0.37295	-0.45956
DR05	0.1549	0.154941	-0.000041
DR06	0.585	0.904623	-0.31962
DR07	0.2218	0.154941	0.066859
DR08	-0.2304	0.036578	-0.26698
DR09	0.3872	0.441283	-0.05408
DR10	0.2924	0.154941	0.137459
DR11	0.1079	-0.37295	0.480845
DR12	0.0362	0.154941	-0.11874
DR13	-0.0791	-0.37295	0.293845
DR14	-0.2041	0.209369	-0.41347
DR15	0.6382	-	-
DR16	-0.3802	-	-
DR17	0.3767	0.032871	0.343829
DR18	0.3098	0.412212	-0.10241
DR19	0.1938	0.294591	-0.10079

DR20	-0.0791	0.028493	-0.10759
DR21	0.4559	0.150493	0.305407
DR22	0.4814	0.032871	0.448529
DR23	-0.0413	-0.18568	0.144377
DR24	-0.2041	-0.20929	0.005189
DR25	-0.4313	-0.70456	0.273262
DR26	-0.8633	-0.48844	-0.37486
DR27	-0.0413	0.30312	-0.34442
DR28	-1.2787	-0.90083	-0.37787
DR29	-0.3802	-0.52599	0.14579
DR30	-0.7993	-0.90083	0.101531
DR31	-1.3222	-1.01919	-0.30301
DR32	-0.5051	-0.90083	0.395731
DR33	-0.9138	-0.90083	-0.01297
DR34	-0.7708	-1.01919	0.248394
DR35	-0.7403	-0.90083	0.160531
DR36	-1.2552	-	-
DR37	-1.4623	-1.01919	-0.44311
DR38	-0.3424	-0.61449	0.272089
DR39	-0.7323	-0.73285	0.000552
DR40	-1.0413	-0.90083	-0.14047
DR41	-0.3802	-0.63689	0.256688
DR42	-0.3222	-0.37295	0.050745
DR43	-0.0413	-0.37295	0.331645
DR44	-0.0413	0.058816	-0.10012
DR45	0.3767	0.295542	0.081158
DR46	-0.0413	0.058816	-0.10012
DR47	0.4814	0.295542	0.185858
DR48	0.602	0.839959	-0.23796
DR49	0.0132	-0.05201	0.065206
DR50	0.9208	0.693638	0.227162
DR51	1.1191	1.284893	-0.16579
DR52	1.2441	1.146778	0.097322
DR53	1.3979	1.403256	-0.00536
DR54	1.4202	1.146778	0.273422
DR55	0.9208	0.791689	0.129111
DR56	0.7958	0.554963	0.240837
DR57	0.7958	0.791689	0.004111
DR58	1	1.292358	-0.29236

All the compounds were within the limit of double the value of r^2se except the compounds DR15, DR16 and DR36. Hence, these compounds were not involved in this model.



Graph 1: Fitness Plot of Model DP1.

REFERENCES

1. Wold, S.; Dunn, W.J. Multivariate quantitative structure activity relationship condition for their application (QSAR). *Journal of Chemical Information and Modeling*, 1983; 23(1): 6-13.
2. Huang, H.J.; Yu, H.W.; Chen, C.Y.; Hsu, C.H.; Chen, H.Y.; Lee, K.J.; Tsai, F.J.; Chen, C.Y.C. Current developments of computer-aided drug design. *Journal of the Taiwan Institute of Chemical Engineers*, 2010; 41(6): 623–635.
3. Winkler, D.A.; Burden, F.R. Bayesian neural nets for modeling in drug discovery. *Drug Discovery Today Biosilico*, 2004; 2(3): 1-8.
4. Bargman, G.J. Insulin the siphon regulator. *Wisconsin Medicinal Journal*, 1975; 74(1): 93-94.
5. Fujimoto, W.Y. Overview of non insulin dependent diabetes mellitus in different population groups. *Diabetes Medicine*, 1996; 13(1): S7-S10.
6. Rother, K.I. Diabetes treatment-bridging the divide. *The New England Journal of Medicine*, 2007; 365(15): 1499-1501.
7. Watkins, P.J. *ABC of Diabetes*, 5th Ed.; BMJ: London, 2003; pp. 32-47.
8. McCarty, M.F. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, diabetes and visceral obesity: Down-regulation with essential fatty acids, ethanol and pentoxifylline. *Medicinal Hypotheses*, 1999; 52(5): 465-477.
9. Iynedjian, P.B. Molecular physiology of mammalian glucokinase. *Cellular and Molecular Life Sciences*, 2009; 66(1): 27–42.

10. Mahalingam, B.; Cuesta-Munoz, A.; Davis, E.A.; Matschinsky, F.M.; Harrison, R.W.; Weber, I.T. Structure model of human glucokinase in complex with glucokinase and ATP: implecations for the mutant that cause hypo and hyperglycemia. *Diabetes*, 1999; 48(9): 1698-1705.
11. Pal, M. Recent advances in glucokinase activators for the treatment of type 2 diabetes. *Drug Discovery Today*, 2009; 14(15/16): 784-792.
12. Heredia, V.V.; Carlson, T.J.; Garcia, E.; Sun, S. Biochemical basis of glucokinase activation and the regulation by glucokinase regulatory protein in naturally occurring mutations. *Journal of Biological Chemistry*, 2006; 281(52): 40201-40207.
13. Mitsuya, M.; Kamata, K.; Bamba, M.; Watanabe, H.; Sasaki, Y.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Nagata, Y.; Eiki, J.; Nishimura, T. Discovery of novel 3,6-disubstituted 2-pyridinecarboxamide derivatives as glucokinase activators. *Bioorganic and Medicinal Chemistry Letters*, 2009; 19(10): 2718-2721.
14. Iino, T.; Tsukahara, T.; Kamata, K.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Hasegawa, T.; Chiba, M.; Nagata, Y.; Eiki, J.; Nishimura, T. Discovery of potent and orally active 3-alkoxy-5-phenoxy-N-thiazolyl benzamides as novel allosteric glucokinase activators. *Bioorganic and Medicinal Chemistry*, 2009; 17(7): 2733–2743.
15. Nishimura, T.; Iino, T.; Mitsuya, M.; Bamba, M.; Watanabe, H.; Tsukahara, D.; Kamata, K.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Futamura, M.; Nagata, Y.; Eiki, J. Identification of novel and potent 2-amino benzamide derivatives as allosteric glucokinase activators. *Bioorganic and Medicinal Chemistry Letters*, 2009; 19(5): 1357–1360.