WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 07, 980-991. Research Article ISSN 2277–7105

STUDY AND DESIGN OF BENZAMIDE AND PYRIDINECARBOXAMIDE DERIVATIVES AS A GLUCOKINASE ACTIVATOR

Dhanraj Patidar[1]*, Sailesh Narayan[1], Rajeev Malviya[1] and Phool Singh Yaduwanshi[2]

[1]Radharaman College of Pharmacy, Ratibad, Bhopal 462048.

[2]IES, College of Pharmacy, Ratibad, Bhopal 462048.

Article Received on
03 Feb. 2018,
Revised on 24 Feb. 2018,
Accepted on 14 March 2018

DOI: 10.20959/wjpr20187-11574

***Corresponding Author**
Dhanraj Patidar
Radharaman College of Pharmacy, Ratibad, Bhopal 462048.

ABSTRACT

Background: The series that was chosen for QSAR studies contained two basic moieties i.e. pyridinecarboxamide and benzamide. 58 compounds were chosen from the published article. **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:** Compound DDR63 was found as the potent compound with EC_{50} value of 1.375µM and the compound DDR73 showed the least potency with EC_{50} value of 19.198µM among the designed compounds. It shows that substitution at 3rd position of thiophenyl with ethoxy group is important for the activity. **Conclusion:** On the basis of descriptors suggested by 2D QSAR, 3D QSAR and 3D show point grid, 33 compounds were designed and their activity was predicted taking 3D model as reference. The compound namely (DDR63) 3-[(3- ethoxyphenyl)sulphonyl]-N- (1,3-thiazol- 2-yl)- 6-(4H- 1,2,4-triazol-3- ylsulfanyl)pyridine-2- carboxamide was found to be the most potent compound among the designed compounds with predicted activity 1.375 µM.

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

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]

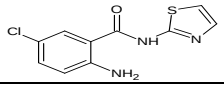
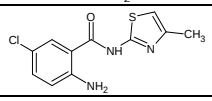
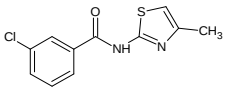
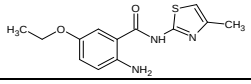
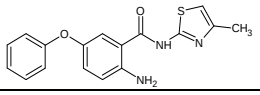
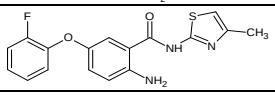
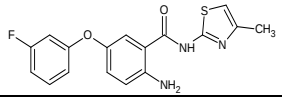
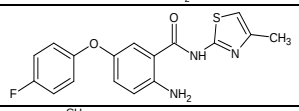
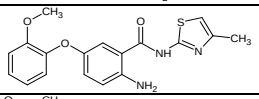
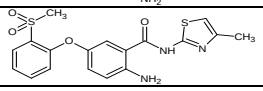
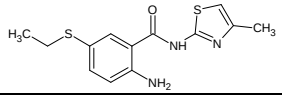
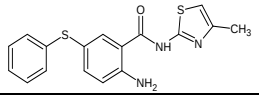
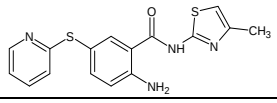
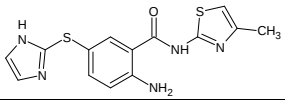
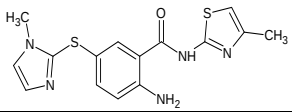
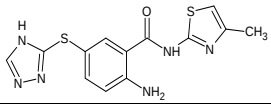
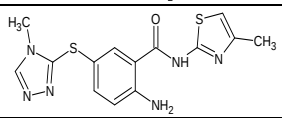
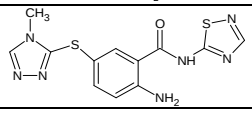
Diabetes mellitus is a group of metabolic disorder in which a person has high blood sugar level due to dysregulation of glucose metabolism, β-cell dysfunction and impaired insulin sensitivity. There are mainly three types of diabetes:- Type 1 diabetes, Type 2 diabetes and Gestational diabetes.[4-8]

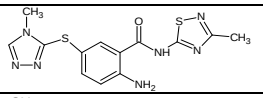
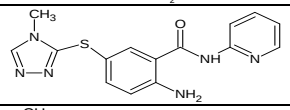
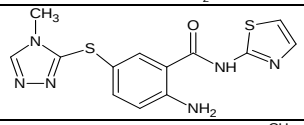
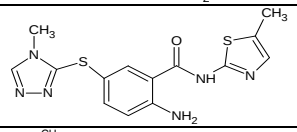
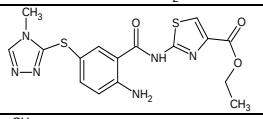
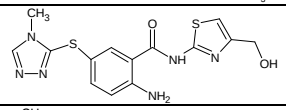
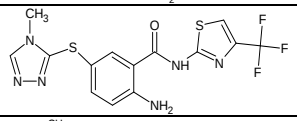
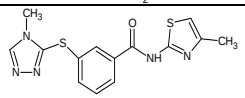
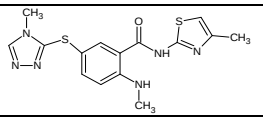
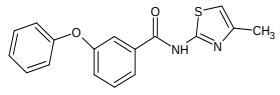
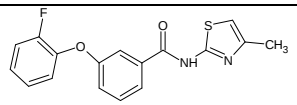
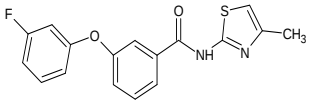
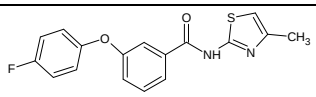
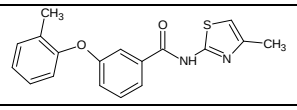
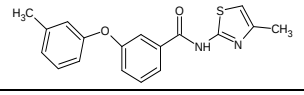
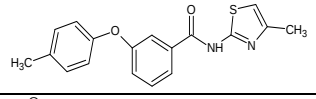
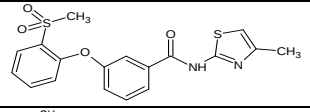
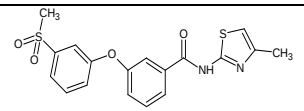
Glucokinase (GK) is an enzyme of the hexokinase family that catalyzes the first step in glycolysis. *Glucokinase* occurs in cells in the liver, pancreas, gut and brain of humans and most other vertebrates and causes phosphorylation of glucose to glucose 6-phosphate. It plays a significant role as a glucose 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]

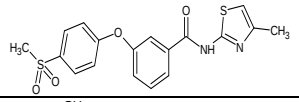
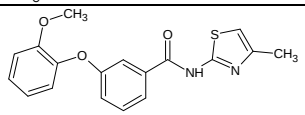
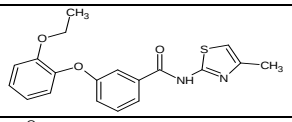
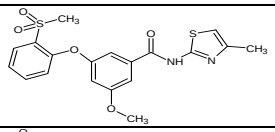
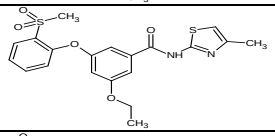
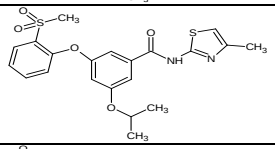
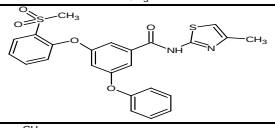
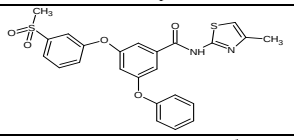
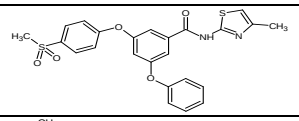
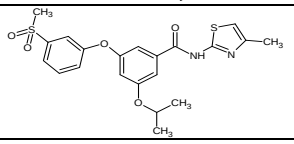
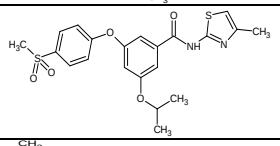
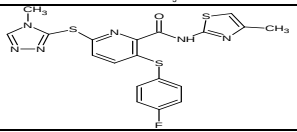
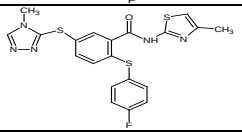
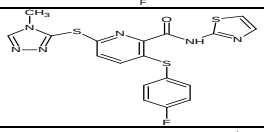
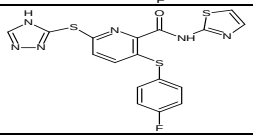
MATERIAL AND METHOD

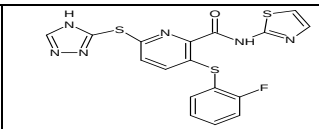
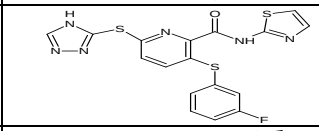
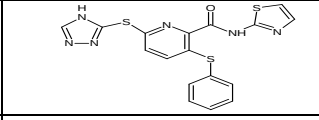
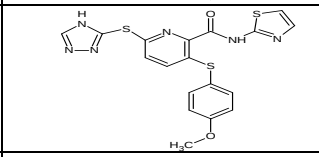
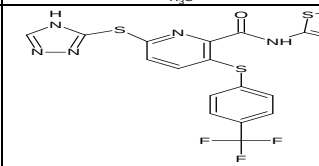
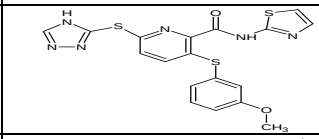
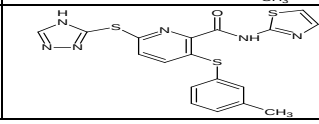
All the computational studies were performed on a Microsoft Window XP running on Pentium-D-processor. QSAR study has been done by using the Vlife MDS software provided by Vlife Sciences Technologies Pvt. Ltd. Pune, India. The series that was chosen for QSAR studies contained two basic moieties i.e. benzamide and pyridinecarboxamide. 58 compounds were chosen from the published article.[13-15] The list of compounds (with their code) and their biological activity is given in table 1.

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 DR47 has highest percentage of optimization and DR02 has lowest percentage of optimization. The majority of compounds showed wide difference in the vdw energy. The highest difference was seen in compound DR09. Apart from vdW energy, bond energy and angle energy has also played role in optimization of some structures. The highest number of cycle required to optimize the molecule is 3036 observed in DR53 where as lowest number of cycles 58 in DR02.

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

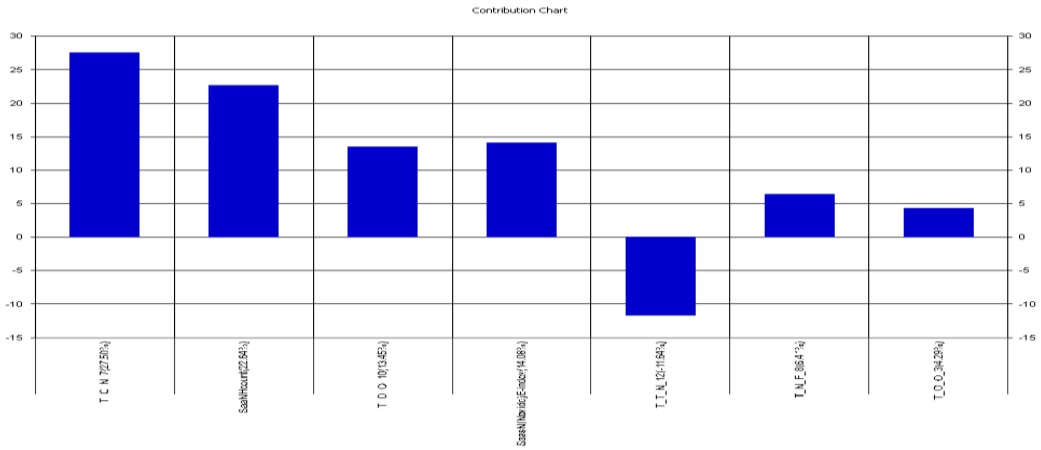
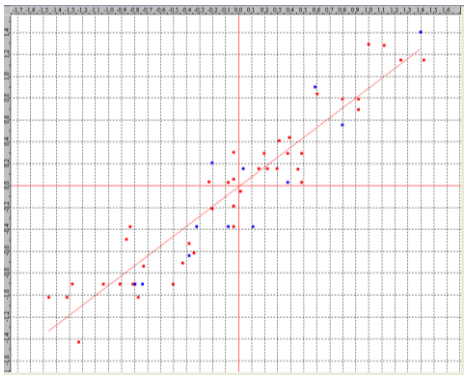
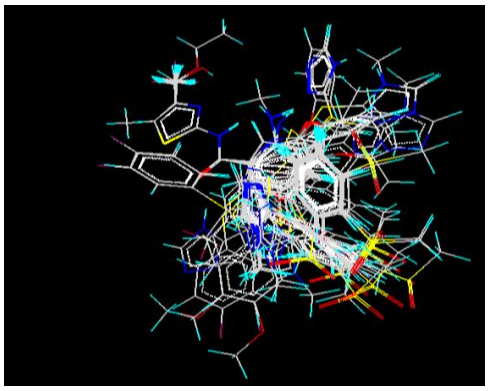


Chart 1: Contribution Chart of Model DP1.

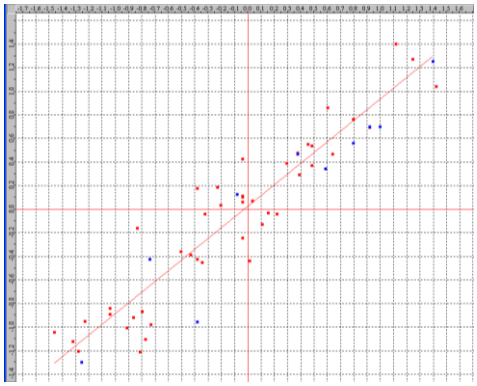
In this model seven descriptors, T_C_N_7, SaaNHcount, T_O_O_10, SaasN(Noxide)E-index, T_T_N_12, T_N_F_8 and T_O_O_3 were found to be highly correlated with biological activity. The descriptor T_C_N_7 showed high contribution (27.50%) in determining the antidiabetic activity. It suggests that increase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



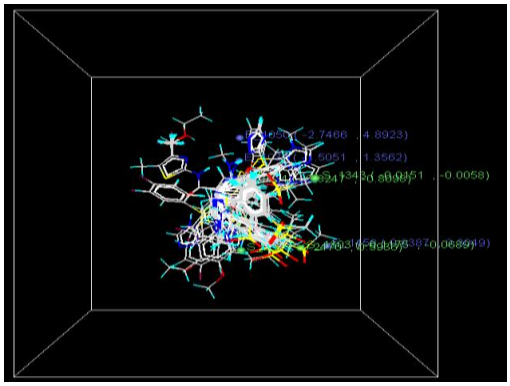
A



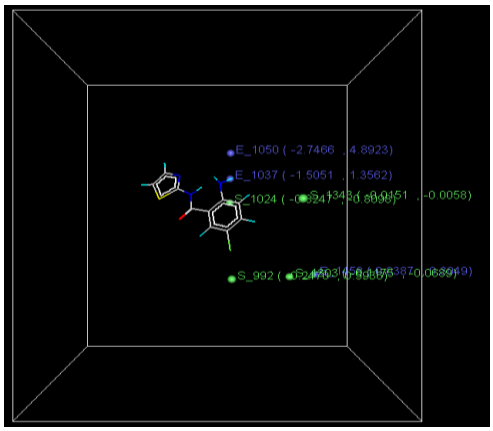
B

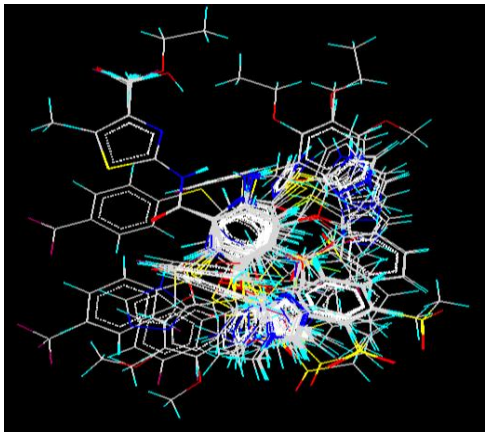


C



D





E **F**

Figure 1: Fitness Plot of Model DP1 (A), Alignment of Compounds by using Template Based Method (B), Fitness Plot of 3D Model (C), Site of Alteration shown in 3D QSAR (D), Site of Alteration on Lead Moiety shown in 3D QSAR (E), Alignment of Designed and 58 Compounds of the Series by usingTemplate Based Method (F)

Lead Moiety used for the Design of Potent *Glucokinase* Activator

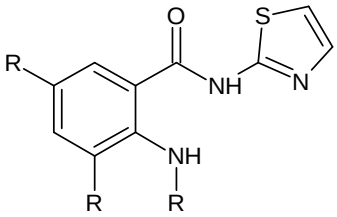
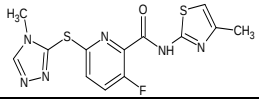
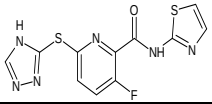
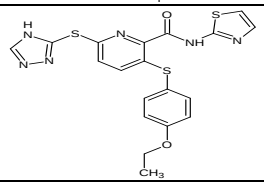
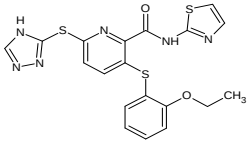
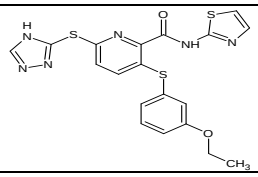
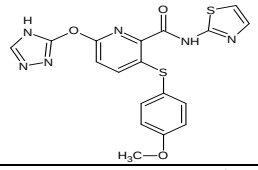
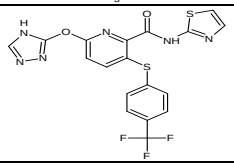
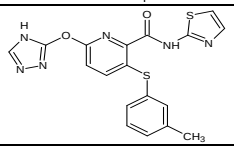
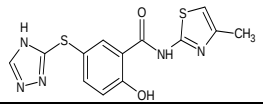
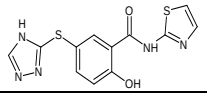
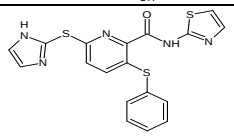
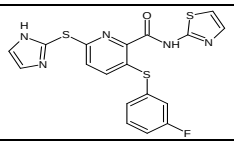
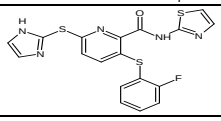
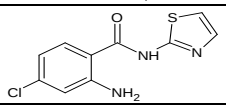
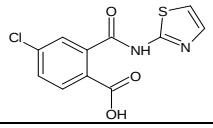
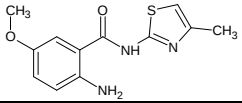
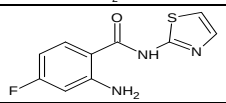
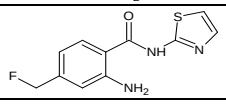
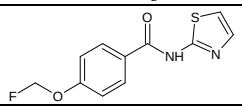
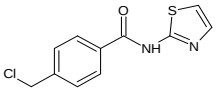
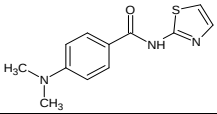
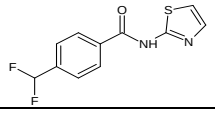
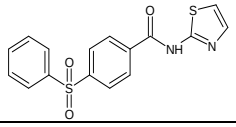
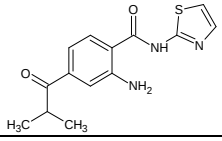
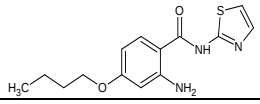
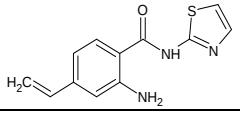
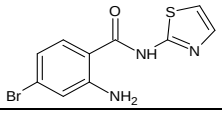
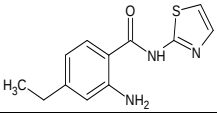
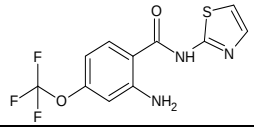
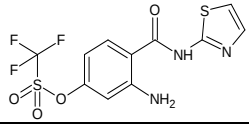
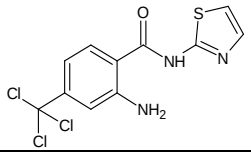
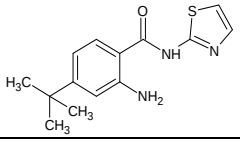
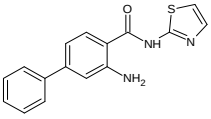


Table 2: Structure and Predicted Activity of the Designed Compounds.

Code	Designing structure	-logEC_{50}	EC_{50} (µM)
DDR59		0.193336	1.560
DDR60		1.266983	18.491
DDR61		0.429202	2.686
DDR62		0.14072	1.382

DDR63		0.138399	1.375
DDR64		1.26908	18.581
DDR65		1.269067	18.580
DDR66		0.145349	1.397
DDR67		1.278818	19.002
DDR68		1.271377	18.680
DDR69		1.272653	18.734
DDR70		1.272704	18.737
DDR71		1.264386	18.381
DDR72		1.278206	18.976
DDR73		1.283267	19.198
DDR74		1.279916	19.050
DDR75		1.278329	18.981
DDR76		1.272882	18.744
DDR77		0.157109	1.435

DDR78		1.276025	18.881
DDR79		1.279362	19.026
DDR80		1.283215	19.196
DDR81		1.282768	19.176
DDR82		1.271417	18.681
DDR83		1.281689	19.128
DDR84		1.277736	18.955
DDR85		1.278159	18.974
DDR86		1.277936	18.964
DDR87		1.278392	18.984
DDR88		1.280347	19.069
DDR89		1.279237	19.021
DDR90		1.277968	18.965
DDR91		1.277409	18.941

From the present QSAR study it is concluded that 2D and 3D QSAR descriptors like T_C_N_7, SaaNHcount, T_O_O_10, SaasN(Noxide)E-index, T_T_N_12, T_N_F_8,

T_O_O_3 and E_1037, E_1458, E_1050, S_992, S_1303, S_1024, S_1343 are highly correlated with biological activity.

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; 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.