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2D-QSAR ANALYSIS OF PHTHALIMIDE DERIVATIVES AS POTENT HYPOGLYCEMIC AGENTS

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ABSTRACT: A quantitative structure activity relationship study on series of total thirty three pthalimide analogues reported compounds was taken. Pthalimide analogues have several advantages over present ant diabetic drugs. The present drugs target insulin resistance and insulin insufficiency. So, it is believed that agents will be available alternative to other second line treatment options including sulfonylurea TZDs, DPP-4 inhibitors. Several statistical regression expressions were obtained using stepwise multiple linear regression analysis (MLR) and partial least square analysis (PLS). Pthalimide analogues activity is described by models that are built on simple 2D molecular descriptors and nevertheless are of good quality and predictive power. The results obtained after performing QSAR were; r^2 = 0.8986, (MLR method) (equation-1), (equation-2) r^2 = 0.6898 (PLS method) The parameters that are found to have significant correlation with hypoglycemic activity are Hosoya Index which is signifies the topological index or Z index, negatively contributing in the biological activity (~40%). The next descriptor is T_N_N_4 i.e. number of Nitrogen atoms (single double or triple bonded) separated from any other Nitrogen atom (single double or triple bonded) by 4 bonds in a molecule. is inversely proportional to the activity (~30%) which mainly indicates the relationship with reference to distance between two nitrogen atoms. The descriptor XK Average Hydrophilicity i.e. Average hydrophilic value also negatively. The r^2 and r (CV) ^{2} values of PCR and PLS models clearly indicate the predictive ability of these models.

INTRODUCTION: A QSAR is a mathematical model or a statistical correlation that relates one or more quantitative parameters derived from chemical structure to a quantitative measure of a property or activity. QSARs are quantitative models yielding a continuous or categorical result.

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The term quantitative in QSAR refers to the nature of the parameter(s) used to make the prediction. The presence of a quantitative parameter enables the development of a quantitative model. Such a model can be used to predict a qualitative or quantitative endpoint. Diabetes, accounts for over 90% of the reported diabetic cases. Most of the current therapies for type 2 diabetes were developed in the absence of defined molecular targets.

Oral hypoglcemics are anti-diabetic drugs designed to help people with type 2 diabetes.

There are seven distinct classes of hypoglycemic agents (**Table 1**): biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, incretin mimetics and DPP-4 inhibitors.[1]

TABLE 1: ORAL HYPOGLYCEMIC DRUGS AND THEIR CLASS

1. Biguanides	Metformin
2. Sulfonylureas	First generation: Acetohexamide Chlorpropamide Tolazamide Tolbutamide Second generation: Glibenclamide/Gliburide Glipizide Glimepiride Gliclazide
3. Meglitinides	Repaglinide Nateglinide
4. Thiazolidinediones	Rosiglitazone Pioglitazone
5. α-Glucosidase inhibitors	Acarbose Miglitol
6. Incretin agonists	Exenatide Liraglutide
7. DPP-4 inhibitors	Sitagliptin Vildagliptin Saxagliptin

1. **Biguanides**: Biguanides are old agents that work by reducing hepatic glucose output and, to a lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues. In contrast to sulfonylureas, metformin does not directly stimulate insulin secretion; its major effects are to increase insulin action and insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver), particularly after meals, and to decrease hepatic glucose output. Moreover, it has an antilipolytic effect that lowers serum free fatty acid concentrations, thereby reducing substrate availability for gluconeogenesis [2].

2. **Sulfonylureas:** Sulfonylureas (tolbutamide) leads to increased mortality due to cardiovascular events, the use of the first generation sulfonylureas (acetohexamide, chlorpropamide, tolbutamide and tolazamide) quickly fell out of favour. In contrast, the second- generation sulfonylureas (glipizide, gliclazide, glibenclamide, called also glyburide) and glimepiride are widely employed worldwide. They work by stimulating insulin release from the insulin secreting ß- cells located in the pancreas [3] and may slightly improve insulin resistance in peripheral target tissues (muscle, fat) [4]. Their receptor is a component of the ATP-dependent potassium channel in the pancreatic β-cells; the binding leads to inhibition of these channels, which alters the resting potential of the cell, leading to calcium influx and stimulation of insulin secretion.

3. **Meglitinides**: The meglitinides, repaglinide and nateglinide, are short-acting glucose-lowering drugs for therapy of patients with type 2 diabetes alone or in combination with metformin. They were designed to achieve more physiologic insulin release and less risk for hypoglycemia. They are structurally different than sulfonylureas but their mechanism of action closely resembles that of sulfonylureas (they act by regulating ATP-dependent potassium channels in pancreatic beta cells), because they stimulate the release of insulin from the pancreatic beta cells through a different binding site on the "sulfonylurea receptor" [5].

4. **Thiazolidinediones**: During the last decade a new class of drugs has been available for treatment of type 2 diabetes: the thiazolidinediones (troglitazone, rosiglitazone and pioglitazone). Actually only two thiazolidinediones (rosiglitazone and pioglitazone) are currently marketed. The majority of data reporting the efficacy of this class comes from studies with troglitazone, results from more recent studies with the newer agents (rosiglitazone and pioglitazone) demonstrating similar properties, although their mechanism of action is not fully understood [6].

   Thiazolinediones improve glycemia reducing insulin resistance and preserving pancreatic beta-cell function with different mechanism of action; as example, the predominant effect of metformin is to inhibit hepatic glucose production, whereas thiazolidinediones act mainly by improving peripheral uptake and utilization of glucose in muscle and fat, finally decreasing liver glucose production [7].

5. **α-Glucosidase Inhibitors**: α-Glucosidase inhibitors include acarbose and miglitol. They act on α-glucosidase, an enzyme found in brush border cells of small intestine, cleaving more complex carbohydrates into sugars.

   α- Glucosidase inhibits the breakdown and absorption of carbohydrates (dextrins, maltose, sucrose and starch; no effect on glucose); their largest impact is on postprandial hyperglycemia and their effect on FPG levels is modest. They have been associated with a reduction in HbA1c by 0.7 to 1.0 percent and FPG levels by 35 to 40 mg per dL (1.9 to 2.2 mmol per L) [8] .

6. **Incretin agonist**: Incretins (Glucagon Like Peptide-1 and Glucose Dependent Insulinotropic Polypeptide) are enteroendocrine hormones released into bloodstream from L and K cells dispersed throughout the gastrointestinal tract [9].

   GLP-1 is secreted in response to nutrients and its levels are decreased in type 2 diabetes; it acts stimulating glucose-dependent insulin release from the pancreatic islets and this is the major advantage over sulfonylureas, as it prevents hypoglycaemia [10].

7. **DPP-4 inhibitors**: DPP-4 rapidly degrades and inactivates GLP-1, GIP, and other peptides in vivo via cleavage of N-terminal two amino acids. Inhibition of this enzyme leads to an increase in circulating endogenous GLP-1 and GIP levels; so that DPP-4 inhibitors are not incretin mimetics, but incretin enhancers. Unlike other GLP-1 based therapies, can be administered orally.

   Sitagliptin, vildagliptin and saxagliptin are DPP-IV inhibitors that are approved as initial pharmacologic therapy for the treatment of type 2 diabetes; as a second agent in those who do not respond to a single agent, such as a sulfonylurea, metformin or a thiazolidinedione; and as a third agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control.

   The usual dose of sitagliptin is 100 mg once daily, with reduction to 50 mg for moderate to severe renal insufficiency (GFR <30 to 50 mL/min) and 25 mg for severe renal insufficiency (<30 mL/min) [11].

OBJECTIVE: The objective of this study is to develop a best suitable model with predictive power. This study helps to determine the hypoglycemic activity of a drug i.e. its biological activity and potency of drug.

MATERIALS & METHODS:

Data Set: The dataset consist of structurally diverse compounds reported for hypoglycemic activity. The selected series comprises of thirty three phthalimide analogues (**Table 1, 2**). The hypoglycemic activity of compounds in the series is reported as Log IC_{50} values refers to experimentally determined concentration required to inhibit 50% of hypoglycemic activity.

The compounds in the selected series were randomly divided into two sets with 25 compounds used as a training set in developing regression models and the remaining 8 as validation set (Test set) in the prediction of biological activity.

2D-QSAR Analysis: The molecular structures of the compounds in selected series were sketched and optimized using V life sciences and were then loaded into a data table within the graphic based QSAR program V life sciences molecular modeling software. The sketched structures were then transferred to three dimensional structures (3D).

The negative logarithm of the original biological activity data were entered into the data table and the entire ranges of molecular properties were calculated using V life sciences technology.

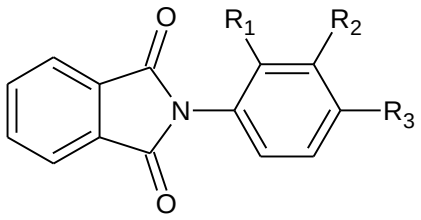
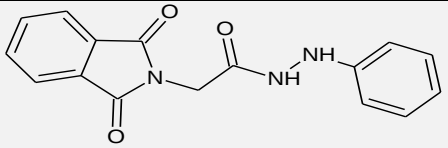
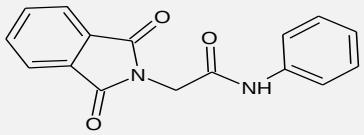
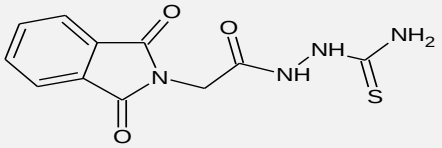
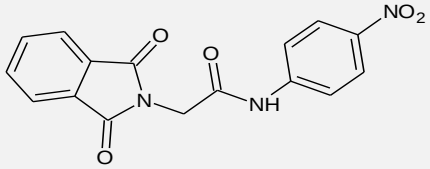
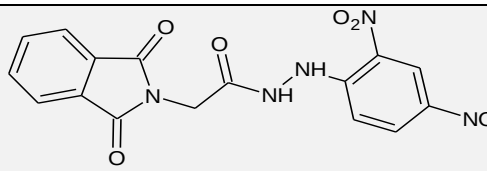
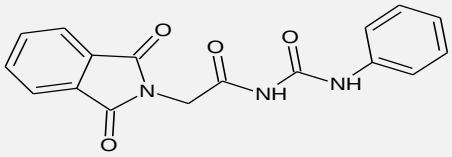
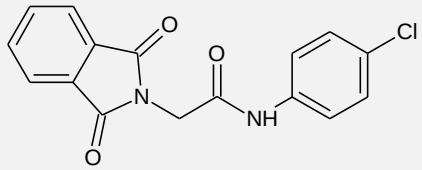
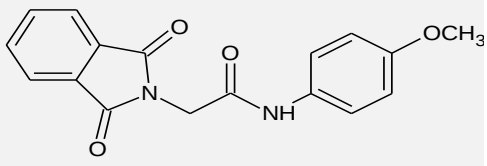


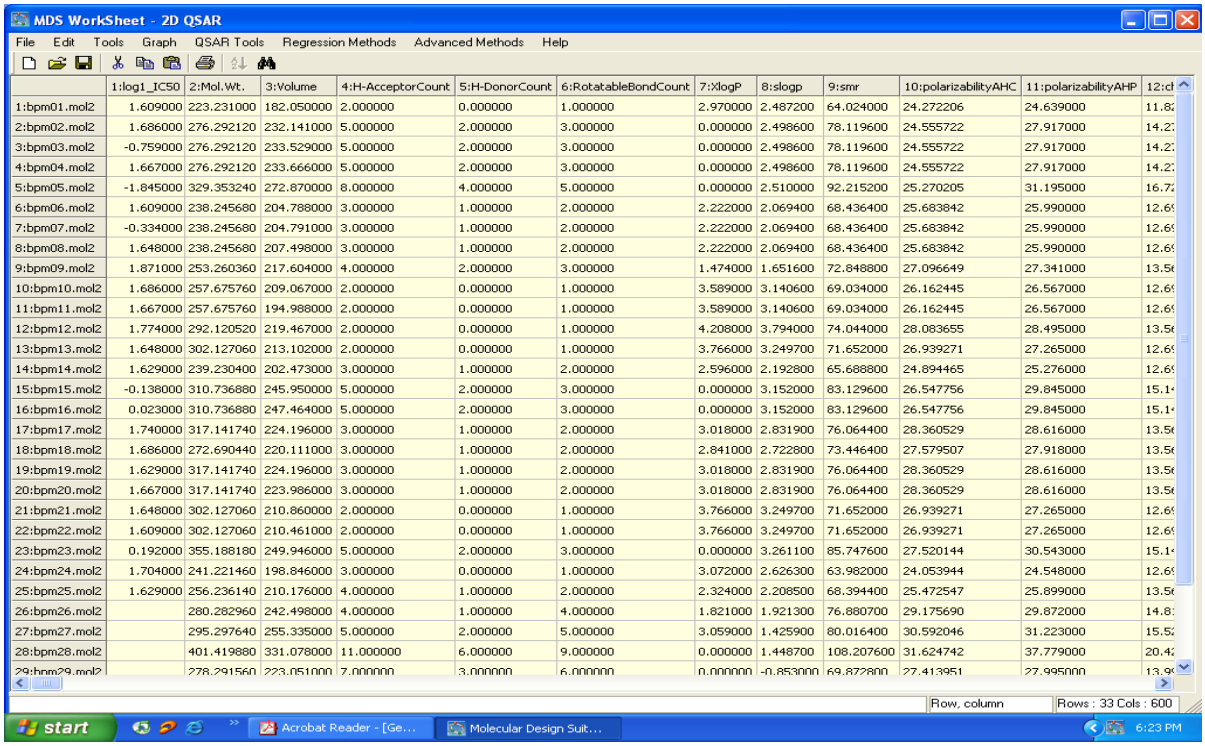
TABLE 1: TRAINING SET WITH BIOLOGICAL ACTIVITY

Compound	R_1	R_2	R_3	Log IC_{50} value
1	H	H	H	1.609
2	NO_2	H	H	1.686
3	H	NO_2	H	-0.759
4	H	H	NO_2	1.667
5	NO_2	H	NO_2	-1845
6	NH_2	H	H	1.609
7	H	NH_2	H	-0.334
8	H	H	NH_2	1.648
9	NH_2	H	NH_2	1.871
10	H	Cl	H	1.686
11	H	H	Cl	1.667
12	Cl	H	Cl	1.774
13	H	Br	H	1.629
14	H	OH	H	1.629
15	NO_2	H	Cl	-0.138
16	Cl	H	NO_2	0.0227
17	NH_2	H	Cl	1.740
18	Cl	H	NH_2	1.686
19	NH_2	H	Br	1.629
20	Br	H	NH_2	1.667
21	H	H	Br	1.648
22	Br	H	H	1.609
23	NO_2	Br	H	0.192
24	H	F	H	1.704
25	NH_2	H	F	1.629

Selection of a series was done of biologically active analogues (training set) with their biological activity. In the table 1, different 25 derivatives with their log IC_{50} are given. Second step was selection of Test set. Table 2 showing the test set (derivative to be synthesized) from 26 to 33, for which the activity will be predicted. Next step was Calculation of various physicochemical parameters. **Figure 1** showing the computer screen for of software for the calculation of physic chemical parameters.

TABLE 2: TEST SET COMPOUNDS

Compound	Structure
26	
27	
28	
29	
30	
31	
32	
33	



	1:log1_IC50	2:Mol.Wt.	3:Volume	4:H-AcceptorCount	5:H-DonorCount	6:RotatableBondCount	7:XlogP	8:slogp	9:smr	10:polarizabilityAHC	11:polarizabilityAHP	12:cl
1:bpm01.mol2	1.609000	223.231000	182.050000	2.000000	0.000000	1.000000	2.970000	2.487200	64.024000	24.272206	24.639000	11.8
2:bpm02.mol2	1.686000	276.292120	232.141000	5.000000	2.000000	3.000000	0.000000	2.498600	78.119600	24.555722	27.917000	14.2
3:bpm03.mol2	-0.759000	276.292120	233.529000	5.000000	2.000000	3.000000	0.000000	2.498600	78.119600	24.555722	27.917000	14.2
4:bpm04.mol2	1.667000	276.292120	233.666000	5.000000	2.000000	3.000000	0.000000	2.498600	78.119600	24.555722	27.917000	14.2
5:bpm05.mol2	-1.845000	329.353240	272.870000	8.000000	4.000000	5.000000	0.000000	2.510000	92.215200	25.270205	31.195000	16.7
6:bpm06.mol2	1.609000	238.245680	204.788000	3.000000	1.000000	2.000000	2.222000	2.069400	68.436400	25.683842	25.990000	12.6
7:bpm07.mol2	-0.334000	238.245680	204.791000	3.000000	1.000000	2.000000	2.222000	2.069400	68.436400	25.683842	25.990000	12.6
8:bpm08.mol2	1.648000	238.245680	207.498000	3.000000	1.000000	2.000000	2.222000	2.069400	68.436400	25.683842	25.990000	12.6
9:bpm09.mol2	1.871000	253.260360	217.604000	4.000000	2.000000	3.000000	1.474000	1.651600	72.848800	27.096649	27.341000	13.5
10:bpm10.mol2	1.686000	257.675760	209.067000	2.000000	0.000000	1.000000	3.589000	3.140600	69.034000	26.162445	26.567000	12.6
11:bpm11.mol2	1.667000	257.675760	194.988000	2.000000	0.000000	1.000000	3.589000	3.140600	69.034000	26.162445	26.567000	12.6
12:bpm12.mol2	1.774000	292.120520	219.467000	2.000000	0.000000	1.000000	4.208000	3.794000	74.044000	28.083655	28.495000	13.5
13:bpm13.mol2	1.648000	302.127060	213.102000	2.000000	0.000000	1.000000	3.766000	3.249700	71.652000	26.939271	27.265000	12.6
14:bpm14.mol2	1.629000	239.230400	202.473000	3.000000	1.000000	2.000000	2.596000	2.192800	65.688800	24.894465	25.276000	12.6
15:bpm15.mol2	-0.138000	310.736880	245.950000	5.000000	2.000000	3.000000	0.000000	3.152000	83.129600	26.547756	29.845000	15.1
16:bpm16.mol2	0.023000	310.736880	247.464000	5.000000	2.000000	3.000000	0.000000	3.152000	83.129600	26.547756	29.845000	15.1
17:bpm17.mol2	1.740000	317.141740	224.196000	3.000000	1.000000	2.000000	3.018000	2.831900	76.064400	28.360529	28.616000	13.5
18:bpm18.mol2	1.686000	272.690440	220.111000	3.000000	1.000000	2.000000	2.841000	2.722800	73.446400	27.579507	27.918000	13.5
19:bpm19.mol2	1.629000	317.141740	224.196000	3.000000	1.000000	2.000000	3.018000	2.831900	76.064400	28.360529	28.616000	13.5
20:bpm20.mol2	1.667000	317.141740	223.986000	3.000000	1.000000	2.000000	3.018000	2.831900	76.064400	28.360529	28.616000	13.5
21:bpm21.mol2	1.648000	302.127060	210.860000	2.000000	0.000000	1.000000	3.766000	3.249700	71.652000	26.939271	27.265000	12.6
22:bpm22.mol2	1.609000	302.127060	210.461000	2.000000	0.000000	1.000000	3.766000	3.249700	71.652000	26.939271	27.265000	12.6
23:bpm23.mol2	0.192000	355.188180	249.946000	5.000000	2.000000	3.000000	0.000000	3.261100	85.747600	27.520144	30.543000	15.1
24:bpm24.mol2	1.704000	241.221460	198.846000	3.000000	0.000000	1.000000	3.072000	2.626300	63.982000	24.053944	24.548000	12.6
25:bpm25.mol2	1.629000	256.236140	210.176000	4.000000	1.000000	2.000000	2.324000	2.208500	68.394400	25.472547	25.899000	13.5
26:bpm26.mol2		280.282960	242.498000	4.000000	1.000000	4.000000	1.821000	1.921300	76.880700	29.175690	29.872000	14.8
27:bpm27.mol2		295.297640	255.335000	5.000000	2.000000	5.000000	3.059000	1.425900	80.016400	30.592046	31.223000	15.5
28:bpm28.mol2		401.419880	331.078000	11.000000	6.000000	9.000000	0.000000	1.448700	108.207600	31.624742	37.779000	20.4
29:bpm29.mol2		278.291560	223.051000	7.000000	3.000000	6.000000	0.000000	-0.853000	69.872800	27.413951	27.995000	13.9

FIGURE 1: WORKSHEET OF TRAINING SET COMPOUNDS WITH THEIR BIOLOGICAL ACTIVITY

TABLE 3: ACTUAL ACTIVITY AND PREDICTED ACTIVITY (A) TRAINING SET (B) TEST SET

Test

Actual	Predicted
0.0000	9.3941
0.0000	-2.1921
0.0000	-33.0712
0.0000	0.2384
0.0000	4.0398
0.0000	6.0589
0.0000	11.6562
0.0000	11.5273

Training

Actual	Predicted
1.6090	1.7179
1.6860	0.9933
-0.7590	-0.3142
1.6670	1.3593
-1.8450	-2.4565
1.6090	1.5778
-0.3340	0.2701
1.6480	1.9438
1.8710	1.7160
1.6860	1.5921
1.6670	1.5850
1.7740	1.3915
1.6480	1.5921
1.6290	1.5921
-0.1380	0.5408
0.0230	0.8852
1.7400	1.3915
1.6860	1.7503
1.6290	1.3915
1.6670	1.7503
1.6480	1.5850
1.6090	1.5778
0.1920	0.5289
1.7040	1.5921
1.6290	1.3915

After that the QSAR equation was generated and the activities of test compounds are predicted.

(a) Model generated by using principal component regression:

$\log IC_{50}$ = - 0.0001 HosoyaIndex - 1.3219 T_N_N_4 - 79.7487 XK Average Hydrophilicity + 0.3588 T_N_N_5 + 2.0090

Optimum Components = 3, n = 25, Degree of freedom = 21, r^2 = 0.8588, q^2 = 0.5669

This is statistically significant model because of r^2 =0.85 (coefficient of determination >0.7) and q^2 =0.56 (cross- validation > 0.5). **Figure 2** showing the contribution chart of different descriptors used in equitation (a) and **table 3** showing the actual and predicted activity of 33 derivatives by using equitation (a).

(b) Model generated by using Multiple regression:

$\log IC_{50}$ = - 0.0000 (±0.0000) Hosoya Index - 1.9775(± 0.0209) T_N_N_4 + 0.7922(± 0.0296) XK Hydrophilic Area + 14.4188(± 4.5621) Most -ve Potential + 3.2401

n = 25, Degree of freedom = 20, r^2 = 0.8986, q^2 = 0.4301

This is statistically not significant model because of r^2 =0.89 (coefficient of determination >0.7) but q^2 =0.43 (cross- validation > 0.5).

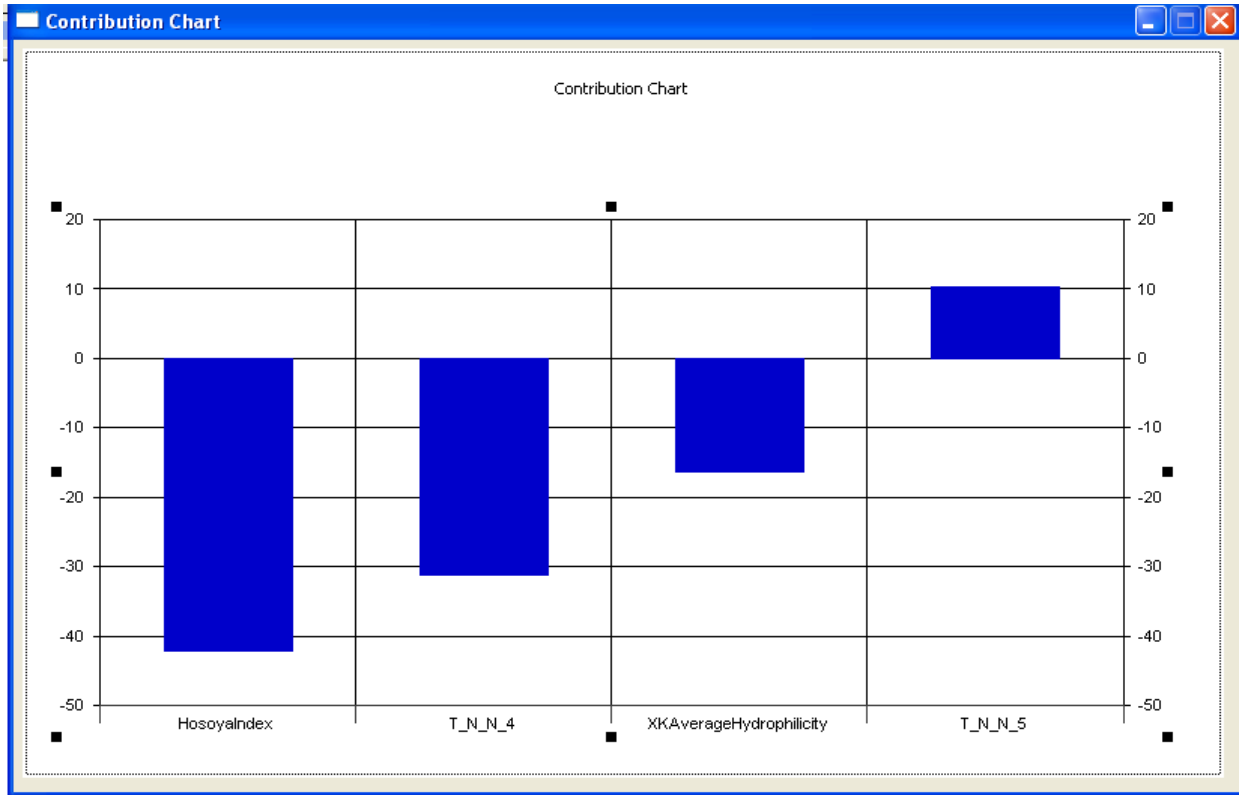


FIGURE 3: CONTRIBUTION CHART FOR MODEL GENERATED BY PCR

(c) Model generated by using Partial Least Squares regression:

$logIC_{50}$ = - 0.0001 HosoyaIndex - 0.4654 T_O_O_7 - 0.0092 XZ Polarizability + 2.0719

Optimum Components = 1, n = 25, Degree of freedom = 23, r^2 = 0.6898, q^2 = 0.5117

This is statistically not significant model because of r^2 =0.68 (coefficient of determination >0.7) but q^2 =0.51 (cross- validation > 0.5).

RESULT & DISCUSSION: The regression coefficient r^2 for the models derived using PCR analysis & PLS analysis were compared together with their corresponding $r(CV)^2$ value.

Result of Principal component regression:

No. of Compounds Under Consideration	r^2	$r(CV)^2$
25	0.85	0.56

CONCLUSION: The regression equation generated in the present study suggests that the chosen properties are equally relevant.

In conclusion the parameters that are found to have significant correlation with hypoglycemic activity are Hosoya Index which is signifies the topological index or Z index, negatively contributing in the biological activity (~40%).

The next descriptor is T_N_N_4 i.e. number of Nitrogen atoms (single double or triple bonded) separated from any other Nitrogen atom (single double or triple bonded) by 4 bonds in a molecule. is inversely proportional to the activity (~30%) which mainly indicates the relationship with reference to distance between two nitrogen atoms. The descriptor XK Average Hydrophilicity i.e. Average hydrophilic value also negatively.

The r^2 and $r(CV)^2$ values of PCR and PLS models clearly indicate the predictive ability of these models. The QSAR studies reveals that the derivative no. 28 would be most active for hypoglycemic activity with predicted $logIC_{50}$ value =-33.074. The derivative no. 27 is next active compound with predicted $logIC_{50}$ value =-2.194 and the third active compound in derivative no. 29 with predicted $logIC_{50}$ value =0.2384.

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