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Insights into Thiazolidinedione Analogues: Unveiling Antioxidant Activity through Descriptor-Based Quantitative Structure-Activity Relationship Investigations

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Diabetes mellitus, a chronic metabolic disorder is characterized by defective insulin secretion (β-cell dysfunction), insulin action (insulin resistance) and reduced bio-antioxidant potential. Antioxidants play key role in diabetes by reducing the oxidative stress and alleviating diabetic complications. Thiazolidinediones (TZDs) attenuate insulin resistance and produce antioxidant effect.

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Study Design: In continuation of our goal to develop thiazolidine-2,4-dione analogues that can address both oxidative stress and Type 2 diabetes, the *in vitro* antioxidant potential of a few synthesized thiazolidinediones (1-61) were evaluated for their DPPH and nitric oxide free radical scavenging assays. Descriptor-based QSAR analysis was utilized to study the structural contribution to the radical scavenging potential.

Results: Among all test compounds, the DPPH radical scavenging activity of compound 12 was found to be significant (IC_{50} 22.7±0.43 µM). The compound 11 (IC_{50}: 13.8±0.5 µM) showed superior nitric oxide radical scavenging potential, when compared to ascorbic acid (IC_{50}: 14.8±0.7 µM). Among various developed QSAR models, 16 and 29 models were found to be best for DPPH and nitric oxide radical scavenging activities, respectively. The R^2 value 0.745 and 0.890 in the above models are indicative of good correlation between *in vitro* and *in silico* antioxidant activity.

Conclusion: The QSAR studies revealed the potential contribution of the partition-coefficient, hydrogen bond acceptor and donors and molecular weight towards the antioxidant activity in both the assay models.

Keywords: Diabetes mellitus; oxidative stress; Knoevenagel condensation; thiazolidine-2,4-dione; molecular descriptor.

1. INTRODUCTION

Diabetes mellitus, a metabolic disease characterized by hyperglycemia associated with long term damage, results in dysfunction and failure of various organs (eyes, kidneys, nerves, heart and blood vessels) [1,2]. The role of oxidative stress (OS) in the pathogenesis of micro and macro vascular complications (retinopathy, nephropathy, atherosclerosis and coronary artery disease) of diabetes is well characterized [3-6]. OS reduces antioxidant enzyme activities by increasing lipid peroxidation and altering glutathione (GSH) redox state. Generation of reactive oxygen species (ROS) such as superoxide anion radicals ($O_2^{-\bullet}$), hydroxyl radicals ($^{\bullet}OH$), etc. is high during diabetes and is involved in the lipid peroxidation. The depleted GSH in OS is responsible for the reduction of the hydrogen peroxide detoxification [6]. Several natural and synthetic antioxidants neutralize ROS by donating their hydrogen and prevent cell damage [7]. The antioxidants reduce oxidative stress and thereby alleviate diabetic complications [8,9]. Oral hypoglycemic agents such as glibenclamide, glipizide and metformin scavenge free radicals and decreases intracellular ROS level [10,11]. Hence, the search for molecules having both hypoglycemic as well as antioxidant potential offers a novel gateway in the diabetes therapy. The Quantitative Structural Activity Relationship (QSAR) studies suggest the importance of quantum- chemical descriptors in producing the antioxidant potential [12,13].

The thiazolidinedione (TZD) class of drugs (pioglitazone and rosiglitazone) attenuate the insulin resistance [14,15]. The antioxidant potential of various 5-substituted-1,3-thiazolidine-2,4-diones and N,5-disubstituted-1,3-thiazolidine-2,4-diones were reported in the literature [16,17]. Prompted by the above mentioned facts, the *in vitro* DPPH and nitric oxide radical scavenging potential of TZDs, 1-61 were evaluated. The descriptor-based QSAR analysis was utilized to identify the molecular properties contributing to the antioxidant activity [18].

2. METHODOLOGY

2.1 Tools

Double-beam Shimadzu UV-Visible spectrophotometer 1800 was used for measuring the absorbance of chromophore formed in both the *in vitro* assay models. The PIC_{50} values were calculated using free Web Sanjeev's lab software. QSAR studies was performed using Strike 1.9 module, (Schrodinger, USA) on Dell Precision T-1500 workstation Intel(R) Core(TM) i7 CPU 860 @ 2.80 GHz; 12.0 GB Ram, 1 TB Hard disk. The structures of the ligands were drawn using Marvin sketch and the geometry was optimized using Ligprep 2.4 (Schrodinger *Inc*).

2.2 Chemistry

The structures of TZDs (1-61) utilized in the present investigation were shown in Figs. 1 and 2 along with their synthetic scheme. The 5-substituted aryl/heteroaryl-1,3-thiazolidine-2,4-diones (1-13) were prepared by Knoevenagel condensation of aryl/heteroaryl aldehydes with 1,3- thiazolidine-2,4-dione. The base catalysed

N-alkylation of thiazolidine-2,4-dione with alkyl halides yielded N-substituted-1,3-thiazolidine-2,4-dione analogues (14-17). Knoevenagel condensation of compounds 14-17 with various arylaldehydes produced N,5-disubstituted-1,3- thiazolidine-2,4-diones (18-49). Reaction of (2,4-dioxo-1,3-thiazolidin-5methylidene) benzene sulphonyl chloride (1a) with various amines and amino acids afforded TZDs 50-61. The synthetic details of compounds 1-61 were described in our previous communications [19-22].

2.3 Evaluation of *in vitro* Antioxidant Activity

The concentration at 50% inhibition (IC_{50}) of a compound is a measure of its potency in inhibiting a specific biological or biochemical function. The test compounds *in vitro* antioxidant potential was determined at various concentrations (10-100 µM). The %inhibition graph for each compound at various tested concentrations was established and the concentration at 50% inhibition (IC_{50}) was determined form the graph in both the in vitro antioxidant activity studies.

2.3.1 DPPH free radical scavenging activity

The DPPH radical scavenging activity of the TZDs, 1-61 was determined by following method given in literature [23]. The test substances of different concentrations (10-100 µM) in dimethyl formamide (2 mL) were added to test tubes containing methanolic DPPH solution (0.3 mM, 1 mL). The mixture was incubated in the dark for 30 min and the absorbance was measured at 517 nm. Reaction mixture without DPPH solution was taken as control. The %DPPH radical scavenging activity of the TZDs was calculated using following formula.

$$\text{DPPH inhibition (\%)} = \frac{\text{Absorbance of control} - \text{Absorbance of test}}{\text{Absorbance of control}}$$

2.3.2 Nitric oxide free radical scavenging activity

The nitric oxide scavenging activity of the synthesized compounds (1-61) was determined by following the literature method with modification [24]. The test/reference compounds (10-100 µM) were incubated with sodium nitroprusside (10 µM) in phosphate buffer pH 7.4 at 25 ^{o}C. After 2½ h, the incubation solution (1 mL) was removed and diluted with Griess reagent (1 mL) and solvent (1 mL). The mixture was kept aside for 20 min. The absorbance of the chromophore formed during diazotization of nitrite with sulphanilamide and subsequent N-napthyl ethylenediamine was measured at 546 nm. The percentage of nitric oxide inhibition was calculated using the given formula and later the values are converted in to IC_{50}.

$$\text{Nitric oxide inhibition (\%)} = \frac{\text{Absorbance of control} - \text{Absorbance of test}}{\text{Absorbance of control}}$$

2.4 Quantitative Structure-Antioxidant Activity Relationship Analysis

All TZDs structures were sketched with Marvin Sketch [25] and geometry optimization was performed with LigPrep 2.4 program [26] using MMFF force field at pH 7±2.0. Molecular properties, such as partition coefficient (Log P), hydrogen bond donors and acceptors (HBD, HBA), energy of highest occupied molecular orbital (HOMO), energy of lowest unoccupied molecular orbital (LUMO), dipole moment (DM), solvent-accessible surface area (SASA), molecular weight (MW), polar surface area (PSA) and molecular volume (MV) were calculated for optimized structures. HOMO and LUMO were determined from MOPAC using the PM3 method. Remaining properties were calculated using quickprop 3.3 [27].

Two data sets containing 33 and 38 TZDs were utilized for quantitative structure-DPPH radical scavenging activity and quantitative structure-nitric oxide radical scavenging activity relationship analysis, respectively. The abovementioned molecular descriptors were considered as the independent variables and the DPPH and nitric oxide radical scavenging activities (PIC_{50}) were considered as the dependent variables. Multiple Linear Regression (MLR) analysis was performed using Strike 1.9 (Schrodinger, 2010). Various QSAR models were generated and were validated by internal validation measures. The DPPH and nitric oxide radical scavenging activity (IC_{50}) of the molecules was converted to corresponding PIC_{50} values using the formula, PIC_{50} = - Log (IC_{50}) [28] and the same values were considered as dependent variable [29].

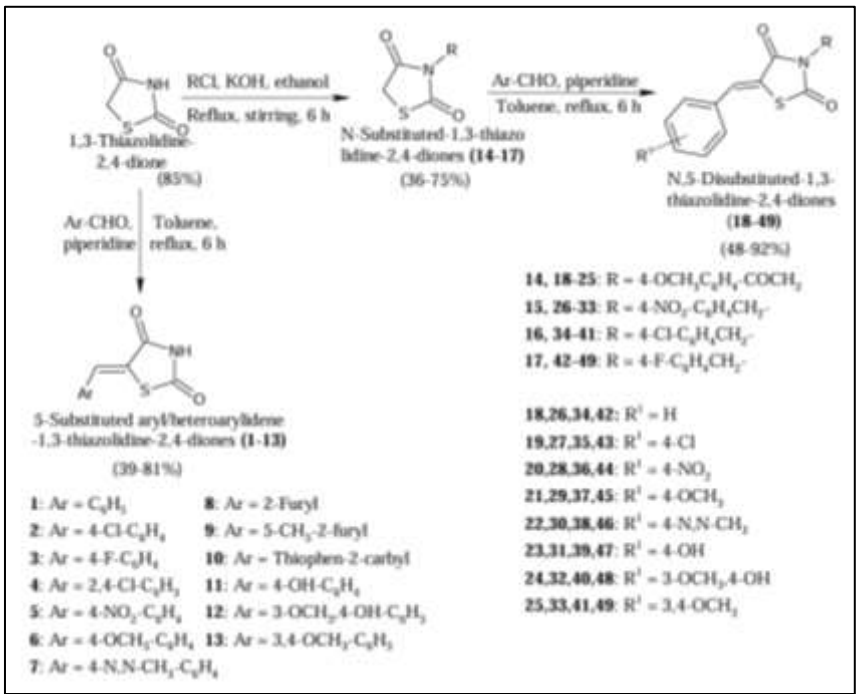

Fig. 1. Scheme showing the synthesis of thiazolidinedione analogues, 1-49

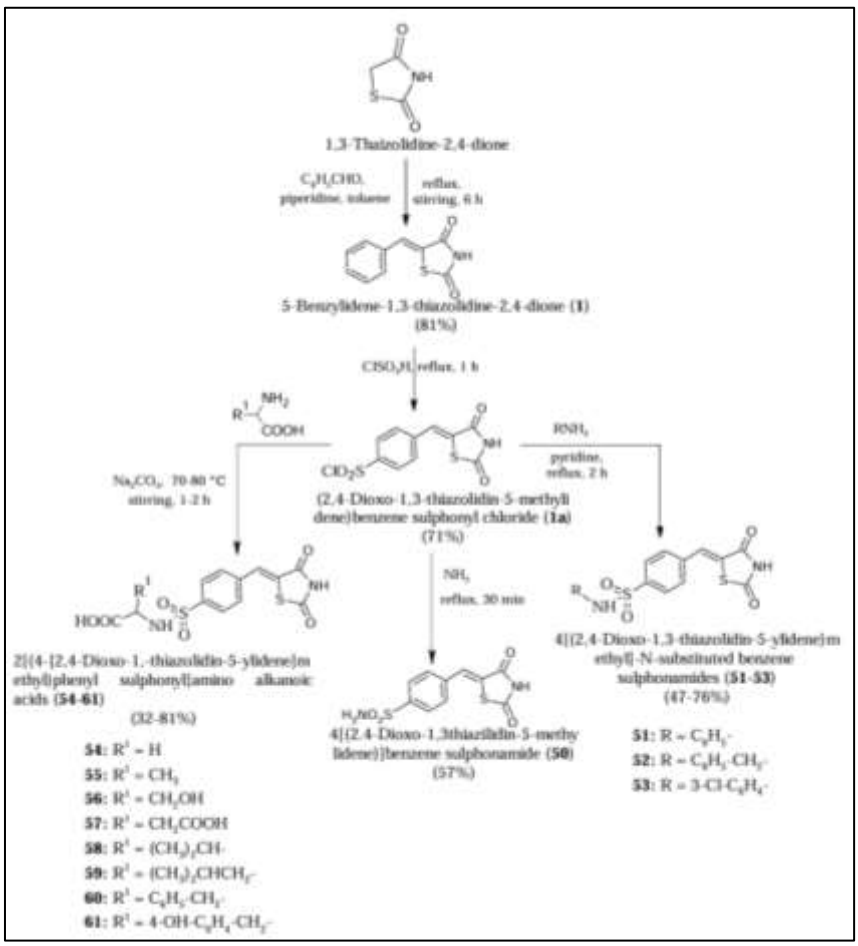

Fig. 2. Scheme showing synthesis of thiazolidinedione analogues, 50-61

3. RESULTS AND DISCUSSION

3.1 Evaluation of Antioxidant Potential

3.1.1 DPPH radical scavenging activity

The TZDs 1-61 were evaluated for their DPPH radical scavenging activity and the results were compared with ascorbic acid, butylated hydroxy anisole and butylated hydroxy toluene. The DPPH radical is reduced by an electron transfer from the antioxidant molecule and, followed by protonation and therefore the colour intensity is decreased. A decrease in the absorbance at 517 nm indicates the DPPH radical scavenging activity of the test compound. The activity was expressed as mean IC_{50} (µM)±SD of triplicate measurements and were given in Table 1. The compound 12 with a *p*-hydroxyl group on the benzylidene ring shown highest DPPH radical

Table 1. *In vitro* radical scavenging activity of compounds

Compound Code	Radical scavenging activity (IC_{50}, µM±SD, n=3)	
	DPPH	Nitric oxide
5	48.7±0.73	93.6±4.9
6	74.6±0.67	72.3±3.8
7	32.1±0.44	65.1±3.8
9	86.4±0.52	97±3.4
11	24.3±0.12	13.8±0.5
12	22.7±0.43	14.3±0.4
13	33.2±0.70	66.2±3.3
14	78.8±0.58	76.9±2.9
15	> 100	86.2±3.9
18	> 100	69.2±3.8
19	> 100	89.1±3.2
20	> 100	73.8±3.6
21	> 100	59.4±2.3
22	33.4±0.24	19±0.4
23	28.1±0.52	14.2±0.7
24	26.3±0.48	14.1±0.5
25	35.5±0.72	56.2±2.5
29	> 100	68.3±3.4
30	68.2±0.66	21.4±1.8
31	29.1±0.57	17.3±0.6
32	29.0±0.52	18.8±1.4
37	> 100	76.2±3.7
38	72.2±0.43	23.8±0.7
39	31.0±0.58	18.7±0.6
40	38.7±0.77	19.2±0.5
41	89.1±0.63	68.1±3.6
45	> 100	81.8±4.9
46	76.4±0.46	25.1±1.6
47	37.8±0.82	18.4±0.6
48	44.3±0.73	19.4±0.8
49	96.4±0.27	68±3.9
50	35.2±1.4	24.5±1.9
52	39.6±2.0	29.3±0.9
54	45.4±1.3	21.8±0.9
55	48.1±1.7	25.3±1.0
56	65.7±2.1	42.4±1.9
57	61.3±2.2	> 100
58	53.6±1.8	34±2.0
Ascorbic acid	13.0±0.48	14.8±0.7
Butylated hydoxy anisole	61[a]	NA
Butylated hydroxyl toluene	220[a]	NA

[a] *Ref 29; NA: Not available*

scavenging activity (22.7±0.43 µM) among the test compounds. It was indicated from this study that the compounds with electron-donating groups showed significant DPPH radical scavenging potential. Compounds with electron-withdrawing (-NO_2 and –Cl) groups and those with unsubstituted benzylidene group on thiazolidinedione ring have shown poor activity (IC_{50} > 100 µM).

3.1.2 Nitric oxide radical scavenging activity

Nitric oxide radical scavenging activity of the TZDs, 1-61 was determined and the results were compared with ascorbic acid (Table 1). Nitric oxide, generated as a result of decomposition of sodium nitroprusside in the aqueous medium, interacts with dissolved oxygen at physiological pH and produce nitrite ions (NO_2^-). Diazotization of sulphanilamide with nitrite in acidic conditions gives a transient diazonium compound which on subsequent coupling with naphthyl ethylenediamine (NED) forms a stable purple azo compound. This chromophore has an absorption maximum at 546 nm. The antioxidant, as it competes with Griess reagent for the nitrite, reduction in the absorbance was observed. The blank without the test substance shows higher absorbance. The TZDs 11, 12, 23 and 24 with strong electron-donating hydroxyl group (IC_{50}: 13.8±0.45, 14.3±0.4, 14.2±0.7 and 14.1±0.5 µM, respectively) showed high nitric oxide inhibitory activity among the test compounds and they were found to be superior to ascorbic acid (IC_{50}: 14.8±0.7 µM). The results indicated the importance of electron-donating functionalities, such as hydroxy (-OH), methoxy (-OCH_3) and N,N-dimethylamino (-N,N-CH_3) groups, as their presence increased the *in vitro* antioxidant activity.

3.2 Development of Descriptor-Based QSAR Model

QSAR analysis was performed to identify the molecular descriptors necessary for the antioxidant activity. It was performed for two different data sets, one utilizing DPPH radical scavenging activity (n=33) and another using nitric oxide scavenging activity (n=38) as dependent variable. Stepwise multiple linear regression analysis method was utilized to perform QSAR analysis. Among the developed models, the best model is selected from various statistically significant equations on the basis of squared correlation coefficient (R^2), standard deviation (SD), sequential Fischer test (*F*) and pearson-r (*P*). The QSAR equation with the lowest SD, and P and the R^2 value reaching to unity is considered as best. A high *F* value explains the strong relation between the variables under study.

3.2.1 Qunatitative structure-DPPH radical scavenging activity relationship analysis

A number of QSAR models were generated by considering the molecular descriptors in different combinations and few of them are given in Table 2. The model 16 with lowest SD (0.146), higher R^2 value (0.743), higher *F* (15.6) and smaller *P* ($3.03x10^{-7}$) values was considered as the best QSAR model. QSAR equation for model 16 in DPPH radical scavenging activity is as follows:

$$PIC_{50} = -2.8472e^{-002} (\pm 5.0088e^{-002}) * Log P + 2.9133e^{-002} (\pm 4.0857e^{-002}) * HBA + 1.8701e^{-001} (\pm 4.6319e^{-002}) * HBD - 1.1159e^{-002} (\pm 2.029e^{-002}) * HOMO + 1.5423e^{-003} (\pm 1.0842e^{-003}) * MW + 2.6244 (\pm 2.7583e^{-001}) \quad (1)$$

n = 33; SD = 0.146; R^2 = 0.745.

A perusal to Table 2 indicated that model 11 is equally a good fit, because it contained four parameters, yet the R^2 value (0.738) was appreciable. Since for calculation of each descriptor 5 to 6 molecules are required, as the present study involves a total of 33 molecules, it would be appropriate to consider the model 16 with five descriptors. The experimental antioxidant activity results were well correlated with the predicted activity (Table 3) with R^2 value of 0.745 (Fig. 3).

The QSAR equation (1) reveals that molecular descriptors like, HBA, HBD and MW were positively contributed, while Log P and HOMO were negatively related to the DPPH radical scavenging activity. The QSAR model was validated internally for its robustness and predictive ability based on the value of leave-one-out cross-validated squared correlation coefficient (LOO-Q^2). The model 16 has shown LOO-Q^2 value of 0.58 (greater than 0.5) and considered to be a good model.

3.2.2 Qunatitative structure-nitric oxide radical scavenging activity relationship analysis

A number of QSAR models were generated by considering the molecular descriptors as

independent variables and nitric oxide radical scavenging activity (PIC_{50}) of compounds as dependent variable. Some of the models were given in Table 4. The model 29 with lowest SD (0.0881), higher R^2 value (0.890), higher *F* (42.1) and smaller *P* ($1.454x10^{-13}$) values was considered as the best QSAR model. The nitric oxide radical scavenging activity of the

Table 2. The statistical relevance of QSAR models in DPPH radical scavenging activity (n=33)

Model No.	Descriptors	SD	R^2	F	P
1	Log P, HBD, MW	0.205	0.451	7.9	$5.115X10^{-4}$
6	Log P, HOMO, MW	0.179	0.584	13.6	$1.02X10^{-5}$
11	Log P, HOMO, MW, HBD	0.144	0.738	19.8	$7.993X10^{-8}$
12	Log P, HOMO, MW, HBA	0.181	0.588	10.0	$3.733X10^{-5}$
16*	Log P, HOMO, MW, HBD, HBA	0.146	0.745	15.6	$3.03X10^{-7}$

**Best model; Log P: Partition coefficient; HBD: Hydrogen bond donor; HBA: Hydrogen bondacceptor; HOMO: Highest occupied molecular orbital; MW: Molecular weight*

Table 3. Experimental and Strike 1.9 predicted DPPH scavenging activity of compounds (n=33)

Compound Code	PIC_{50}[a]		Residual[c]
	Experimental	Predicted [b]	
5	4.31	4.40	-0.09
6	4.13	4.25	-0.12
7	4.49	4.21	0.28
9	4.07	4.20	-0.13
11	4.61	4.44	0.17
12	4.66	4.49	0.17
13	4.48	4.33	0.15
14	4.11	4.23	-0.12
22	4.48	4.28	0.2
23	4.55	4.50	0.05
24	4.59	4.59	0
25	4.46	4.38	0.08
30	4.17	4.3	-0.06
31	4.53	4.46	0.07
32	4.56	4.52	0.04
38	4.14	4.13	0.01
39	4.51	4.36	0.15
40	4.42	4.43	-0.01
41	4.05	4.23	-0.18
46	4.12	4.12	0
47	4.43	4.35	0.08
48	4.36	4.41	-0.05
49	4.02	4.22	-0.2
50	4.68	4.74	-0.06
52	4.86	4.93	-0.07
54	4.42	4.45	-0.03
55	4.41	4.43	-0.02
56	4.44	4.48	-0.04
57	4.33	4.32	0.01
58	4.74	4.76	-0.02
Ascorbic acid	4.89	4.99	-0.1
Butylated hydoxy anisole	4.21	4.01	0.2
Butylated hydroxyl toluene	3.66	4.02	-0.36

[a] PIC_{50} = -(Log IC_{50}); [b] Predicted activity values as per model 16 inTable 2. [c] Residual = Experimental activity - Predicted activity

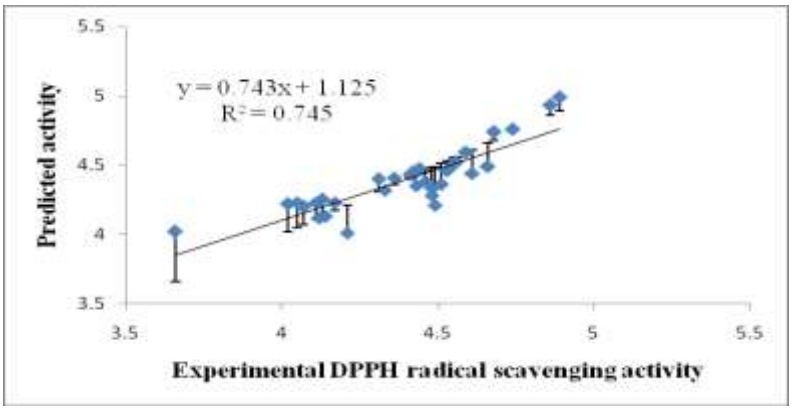

Fig. 3. A plot showing experimental versus predicted DPPH radical scavenging activity of TZDs (n=33) with residual representation using QSAR model

Table 4. The statistical relevance of QSAR models in nitric oxide radical scavenging activity(n=38)

Model No.	Descriptors	SD	R^2	F	P
2	Log P, HBD, MV	0.102	0.839	59.0	$1.458X10^{-13}$
9	Log P, HBD, MW, HBA	0.103	0.84	43.4	$1.087X10^{-12}$
14	Log P, HBD, MV, DM	0.0946	0.866	53.2	$6.214X10^{-14}$
23	Log P, HBD, DM, HBA, MV	0.0931	0.874	44.4	$1.810x10^{-13}$
29*	Log P, HBD, DM, HBA, MV, MW	0.0881	0.890	42.1	$1.454x10^{-13}$

**Best model; Log P: Partition coefficient; HBD: Hydrogen bond donor; HBA: Hydrogen bondacceptor; DM: Dipole moment; MV: Molecular volume; MW: Molecular weight*

TZDs (as represented by PIC_{50}) is best predicted by regression equation (2). It evidences the positive contribution of Log P, HBD, DM and MV and negative contribution of HBA and MW towards the nitric oxide radical scavenging activity.

PIC_{50} = $1.5849e^{-002}$ ($\pm 4.9755e^{-002}$)*Log P- $8.6896e^{-002}$ ($\pm 3.5278e^{-002}$)*HBA +$3.9092e^{-001}$($\pm 2.5836e^{-002}$) *HBD+$4.9026e^{-003}$ ($\pm 9.5644e^{-003}$)*DM- $4.4276e^{-003}$ ($\pm 2.0299e^{-003}$)*MW+$2.620e^{-003}$ ($\pm 9.8161e^{-004}$) *MV+ $3.4047e^{+000}$($\pm 1.2392e^{-001}$) (2)

n = 38; R^2 = 0.890; SD = 0.0881.

The experimental antioxidant activity results were well correlated with the predicted activity (Table 5) with R^2 value of 0.890 (Fig. 4). The model 29 has shown LOO-Q^2 value of 0.8385 (greater than 0.5) and thus the model was predicted to be good.

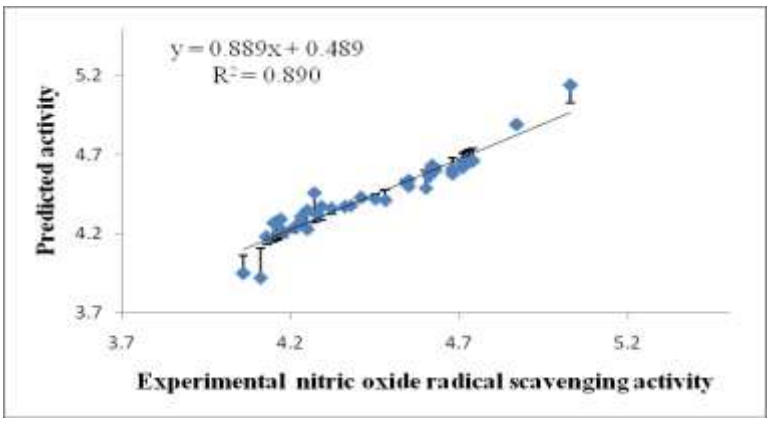

Fig. 4. A plot showing experimental versus predicted nitric oxide radical scavenging activity of TZDs (n=38) with residual representation using QSAR model

Table 5. Experimental and Strike 1.9 predicted nitric oxide radical scavenging activity of compounds (n=38)

Compound Code	PIC_{50}[a]		Residual[c]
	Experimental	Predicted [b]	
5	4.18	4.21	-0.03
6	4.28	4.32	-0.04
7	4.27	4.46	-019
9	4.15	4.27	-0.12
11	4.71	4.62	0.09
12	4.68	4.61	0.07
13	4.23	4.31	-0.08
14	4.11	3.92	0.19
15	4.06	3.95	0.11
18	4.16	4.28	-0.12
19	4.21	4.24	-0.03
20	4.13	4.18	-0.05
21	4.23	4.28	-0.05
22	4.48	4.41	0.07
23	4.68	4.58	0.1
24	4.61	4.56	0.05
25	4.25	4.23	0.02
29	4.17	4.29	-0.12
30	4.41	4.43	-0.02
31	4.63	4.60	0.03
32	4,61	4.59	0.02
37	4.32	4.36	-0.04
38	4.55	4.50	0.05
39	4.73	4.66	0.07
40	4.72	4.65	0.07
41	4.36	4.37	-0.01
45	4.25	4.35	-0.1
46	4.6	4.49	0.11
47	4.74	4.66	0.08
48	4.71	4.65	0.06
49	4.29	4.37	-0.08
50	4.62	4.63	-0.01
52	4.54	4.52	0.02
54	4.45	4.42	0.03
55	4.55	4.54	0.01
56	4.38	4.38	0
58	5.03	5.14	-0.11
Ascorbic acid	4.87	4.89	-0.02

[a] PIC_{50} = -(Log IC_{50}); [b] Predicted activity values as per model 29 inTable 4. [c] Residual = Experimental activity - Predicted activity

4. CONCLUSION

The antioxidant potential of few TZDs (1-61) was assessed by *in vitro* DPPH and nitric oxide radical scavenging activities. The statistical relevance between molecular descriptors and antioxidant activity was established through descriptor-based QSAR analysis. The compounds with electron-donating groups at the benzylidene portion of the analogues have shown predominant antioxidant activity in comparison of molecules with electron-withdrawing groups. The QSAR studies revealed the contribution of hydrophobic (Log P), electronic (HBD, HBA, HOMO and DM) and steric (MW) descriptors towards the antioxidant activity. in both the *in vitro* antioxidant assays, compounds 11, 12, 23 and 24 showed significant radical scavenging activities in comparison with reference compounds. The difference between experimental and predicted activity data (residual) of the above compounds

was also small. From these findings, compounds 11, 12, 23 and 24 were identified as potential leads for the further synthesis of analogues and *in vivo* investigations.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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