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QSAR studies on imidazoles and sulfonamides as antidiabetic agents

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Abstract. The main objective of the present study was to establish significant and validated QSAR models for imidazoles and sulfonamides to explore the relationship between their physicochemical properties and antidiabetic activity. Two dimensional QSAR models had been developed by multiple linear regression and partial least square analysis methods, and then validated for internal and external predictions. The established 2D QSAR models were statistically significant and highly predictive. The validation methods provided significant statistical parameters with $q^2 > 0.5$ and pred_$r^2 > 0.6$, which proved the predictive power of the models. The developed 2D QSAR models revealed the significance of SlogP and T_N_O_5, and Mol.Wt and SsBrE-index properties of imidazoles and sulfonamides on their antidiabetic activity, respectively. These results should prove to be an essential guide for the further design and development of new imidazoles and sulfonamides having better antidiabetic activity.

Keywords: antidiabetic, physicochemical properties, QSAR, validation.

1. Introduction

The discovery and development of a new chemical entity with demonstrated utility in ameliorating or curing disease is a long and arduous process. Industry statistics suggests that up to several thousand compounds are synthesized and tested; up to 100 compounds are assessed for safety; and up to 10 compounds are tested clinically in humans for every drug that is approved for medical use. Trial and error screening used to consider as the normal procedure, is becoming very costly and at the same time less efficient. Therefore, only molecules with good chance of activity should be prepared and tested. In this context, proper designing is required before synthesis of the drugs.

Diabetes is a complex and costly disease that can affect nearly every organ in the body and result in devastating consequences [1]. Diabetes is the major causes of renal failure, blindness [2], stroke, cardiovascular disease, premature and perinatal mortality [3]. Insulin is the choice of treatment for type 1 diabetes. Type 2 diabetes can be managed with a combination of different oral and injectable antidiabetic agents [4].

In rational drug design, numerous 2D QSAR studies [5-10], 3D QSAR studies [11, 12] and binding studies [13] have been reported for different group of chemical derivatives and their antidiabetic activity. With the aim of developing good antidiabetic drugs, we have selected some imidazole and sulfonamide antidiabetic compounds [14-17] to understand structural insight, which is responsible for selectivity of these derivatives towards diabetes by using QSAR analysis. The series of compounds had shown well defined activity. There was high structural diversity and a sufficient range of the biological activity in the series of compounds selected for the present study. The developed QSAR models were statistically significant and could efficiently guide to design imidazole and sulfonamide derivatives with better antidiabetic potential.

2. Experimental

2.1. Software

CS Chem Office 2004 (Cambridge Soft Corp., Cambridge, USA, http://www. cambridgesoft.com) and the molecular modeling studies were carried out in Vlife MDS 4.3 (VLife Sci Tech Private Ltd, India, www.vlifesciences.com).

2.2. Sketching of molecules

The .mol files of structures (Imidazole and sulfonamide antidiabetic compounds [14-17]), which were drawn and cleaned up in Chem 3D, were transferred to VLife MDS.

2.3. Energy minimization

"The geometry of the 3D structures was optimized to local minima by Merck Molecular Force Field (MMFF) by considering distance-dependent dielectric constant of 1.0, convergence criterion or root-mean-square (RMS) gradient at 0.001 kcal/mol Å and the iteration limit to 10,000. Most stable structure for each compound was generated and saved as .mol2 files for computing various physico-chemical and alignment independent descriptors" [18].

2.4. Calculation of descriptor (Independent variable)

The energy-minimized structures were used for the calculation of the various 2D descriptors like physico-chemical (200 in numbers) and other alignment independent descriptors (700 in numbers). The preprocessing of the independent variables (i.e., 2D descriptors) was done by removing invariables and variable exclusion was done for constant variable or near constant variable at paired correlation. Finally all

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together 300 descriptors were selected to develop models.

2.5. Training and test set selection

Division of compounds into training and test data set was done by using sphere exclusion (SE) and random selection methods. The dissimilarity value 1 and 1.5 was used in sphere exclusion method, where the dissimilarity value is the sphere exclusion radius. In random selection method selection of training set compounds with four trials 70, 75, 80 and 85% were tried [19]. The reported IC_{50} or Ki values of the selected series of compounds for the present QSAR study as their negative logarithmic concentrations [$-\log IC_{50}$ or pIC_{50} or pKi], where IC_{50} is the micro molar concentration of the compounds producing 50% inhibition in the glucagon receptor activity [14] and Ki is carbonic anhydrase II inhibitor activity [15-17].

2.6. Feature selection and model development

In the present study, stepwise (SW) forward–backward variable selection [20], genetic algorithms (GA) [21] and simulated annealing (SA) [22] based feature selection procedures were used to build QSAR models. The cross-correlation limit 0.5, the number of variables 5, and the term selection criteria q^2 was used to build QSAR models. The variance cutoff of 0 and auto-scaling with number of random iterations 100 was used to normalize the independent variables.

The stepping criteria for inclusion of predictor variable F = 4 and exclusion of predictor variable F = 3.99 was used in SW forward-backward variable selection algorithm. Population 10, number of generations 1000 and speed of 9999 was used in GA method. The maximum and minimum temperature used in SA method was 100 K and 0.01 K, and it was decreased by 5 units with 100 iterations at that particular temperature [18].

Multiple linear regression and partial least square analysis were used to find the relation between the dependent and independent variables. The relationship between dependent variable and various independent variables were established by using QSAR module of VLife MDS software.

2.7. Model quality and validation

The developed QSAR models are evaluated using the following statistical measures: n (the number of compounds in regression); k (number of variables); DF (degree of freedom); r^2 (squared correlation coefficient); r^2se (standard error of r^2); F test (Fischer's value); q^2 (cross-validated squared correlation coefficient); q^2_se (standard error of q^2); $pred\_r^2$ (r^2 for external test set); $pred\_r^2se$ (standard error of $pred\_r^2$); Z score (Z score calculated by the randomization test); $best\_ran\_q^2$ (highest q^2 value in the randomization test); $best\_ran\_r^2$ (highest r^2 value in the randomization test). A QSAR model is considered to be predictive, if the following conditions are satisfied: $r^2 > 0.7$, $q^2 > 0.5$ and $pred\_r^2 > 0.6$ [23]. The quality and validation parameters of QSAR models are compiled and discussed in detail somewhere by Ravichandran *et al.* [24].

3. Results and discussion

Series I: Triaryl imidazoles

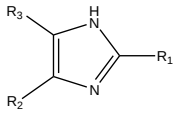
The glucagon antagonist activity and structure of 27 compounds (Table 1) was taken from the study reported by Chang *et al*. after excluding 11 molecules which were not having a well-defined biological activity, and 3 molecules that are not congeners to the rest of the dataset [14]. Different feature selection and model development methods were used to develop 2D QSAR models. One of the best developed models was Eq. (1). The criteria's used to get this model were: random training and test set selection method (70%), stepwise forward-backward variable selection method, model development by multiple linear regression (MLR), test set compounds: **4**, **5**, **7**, **10**, **15**, **16**, **21**, **25**, and outliers: compound **8**.

$pIC_{50} = 1.923 + 0.753\ (\pm 0.062)\ SlogP + 0.591\ (\pm 0.201)\ T\_N\_O\_5$ Eq. (1)

$n = 18$, $r^2 = 0.917$, $r^2se = 0.302$, $q^2 = 0.880$, $q^2se = 0.364$, $F_{2,15} = 83.191$, $pred\_r^2 = 0.830$, $pred\_r^2\ se = 0.425$, Z Score $r^2 = 8.681$, Z Score $q^2 = 7.563$, Best Rand $r^2 = 0.387$, Best Rand $q^2 = 0.138$

Eq. (1) could explain 91.7% and predict 83.0% of the variance of the antidiabetic data. There was no inter-correlation between the descriptors. The parameters involved in the selected model (SlogP, T_N_O_5) and the calculated antidiabetic activity by Eq. (1) are given in Table 2.

Table 1. The structures of triaryl imidazoles with their glucagons antagonist activity



Compounds	R_1	R_2	R_3	pIC_{50}
1	(4-Br)Ph	(4-F)Ph	4-pyridyl	6.569
2	(3-Br)Ph	(4-F)Ph	4-pyridyl	5.854
3	(4-Cl)Ph	(4-F)Ph	4-pyridyl	6.398
4	(4-F)Ph	(4-F)Ph	4-pyridyl	5.699
5	(4-I)Ph	(4-F)Ph	4-pyridyl	6.292
6	(4-Me)Ph	(4-F)Ph	4-pyridyl	5.886
7	(4-*i*Pr)Ph	(4-F)Ph	4-pyridyl	6.155
8	(4-Ph)Ph	(4-F)Ph	4-pyridyl	5.000
9	(4-NH_2)Ph	(4-F)Ph	4-pyridyl	5.699

Compounds	R_1	R_2	R_3	pIC_{50}
10	(4-OMe)Ph	(4-F)Ph	4-pyridyl	4.886
11	(4-CN)Ph	(4-F)Ph	4-pyridyl	5.097
12	(4-COOMe)Ph	(4-F)Ph	4-pyridyl	5.060
13	(4-SMe)Ph	(4-F)Ph	4-pyridyl	6.310
14	(4-Br)Ph	Ph	4-pyridyl	6.107
15	(4-Cl)Ph	(4-F)Ph	3-Me(4-pyridyl)	5.959
16	(4-Cl)Ph	(4-Cl)Ph	4-pyridyl	6.721
17	(4-Cl)Ph	(4-I)Ph	4-pyridyl	6.886
18	(4-Cl)Ph	(4-Ph)Ph	4-pyridyl	6.854
19	(4-Cl)Ph	(4-t-Bu)Ph	4-pyridyl	6.886
20	(4-Cl)Ph	(4-n-Bu)Ph	4-pyridyl	7.131
21	(4-Cl)Ph	(3-Ph)Ph	4-pyridyl	7.215
22	(4-Cl)Ph	(2-OPh)Ph	4-pyridyl	8.187
23	(4-Cl)Ph	(3-OPh)Ph	4-pyridyl	7.886
24	(4-Cl)Ph	(4-OPh)Ph	4-pyridyl	7.569
25	(4-Cl)Ph	(2-O-n-Bu)Ph	4-pyridyl	8.071
26	(4-Cl)Ph	(2,4-(O-n-Pr)$_2$)Ph	4-pyridyl	7.886
27	(4-Cl)Ph	(2,4-(O-n-Bu)$_2$)Ph	4-pyridyl	8.187

Table 2. Descriptors involved in 2D QSAR model Eq. (1) for glucagons receptor antagonistic activity of triaryl imidazoles and their predicted activity

Compounds	SlogP	T_N_O_5	Actual activity (pIC_{50})	Predicted activity (pIC_{50})
1	5.707	0	6.569	6.217
2	5.707	0	5.854	6.217
3	5.598	0	6.398	6.135
4[a]	5.084	0	5.699	5.749
5[a]	5.549	0	6.292	6.099
6	5.253	0	5.886	5.876
7[a]	6.068	0	6.155	6.489
8	6.612	0	*	*
9	4.527	0	5.699	5.330
10[a]	4.953	0	4.886	5.650
11	4.816	0	5.097	5.547
12	4.731	0	5.06	5.483
13	5.667	0	6.31	6.187
14	5.568	0	6.107	6.113
15[a]	5.907	0	5.959	6.368
16[a]	6.112	0	6.721	6.522
17	6.064	0	6.886	6.486
18	7.126	0	6.854	7.285
19	6.757	0	6.886	7.008
20	6.802	0	7.131	7.041
21[a]	7.126	0	7.215	7.285
22	7.251	1	8.187	7.970
23	7.251	1	7.886	7.970
24	7.251	0	7.569	7.379
25[a]	6.638	1	8.071	7.509
26	7.037	1	7.886	7.809
27	7.817	1	8.187	8.396

[a] – indicates test set compounds, * - indicates outliers

The correlation of experimental activity against predicted activities by Eq. (1) is graphically represented in Figure 1. The closeness of the actual and predicted activity by Eq. (1) for training and test set compounds are shown in Figure 2 and 3, respectively.

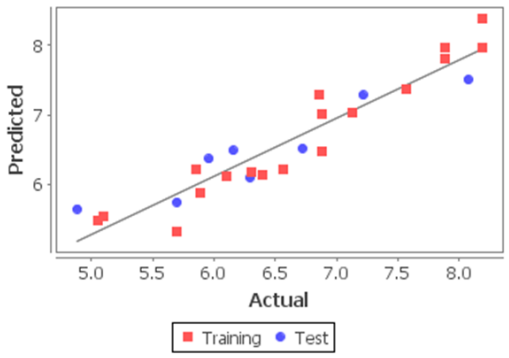


Figure 1. Fitness plot between the experimental and predicted activities by Eq. (1)

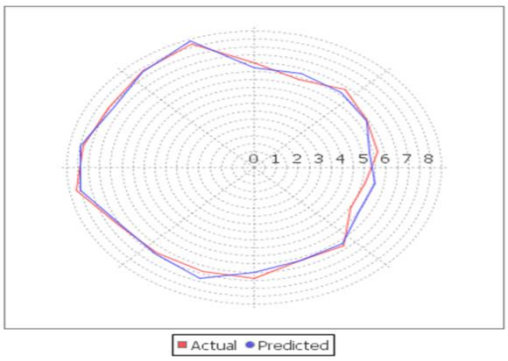


Figure 2. Radar plot depicting closeness between the actual and predicted activity of training set compounds by Eq. (1)

The selected model was good in internal prediction (q^2 = 0.880) and external prediction (pred_r^2 = 0.830). The good results in our original model are not due to a chance correlation or structural dependency of the compounds was buttressed by the low randomized r^2 (0.287) and q^2 (0.138) values.

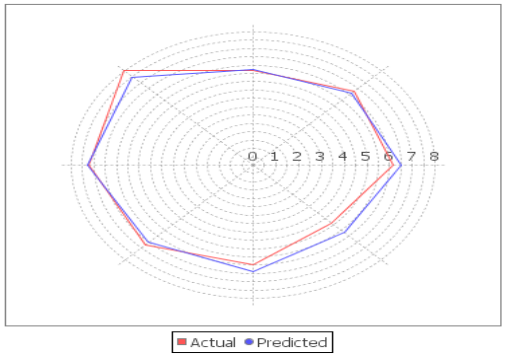


Figure 3. Radar plot depicting closeness between the actual and predicted activity of test set compounds by Eq. (1)

The developed MLR model reveals that the descriptor T_N_O_5 which is an alignment independent descriptor showed positive contribution. Such positive effect indicates that the antidiabetic activity is increased with increase in the count of number of nitrogen atom (single, double or triple bonded) separated from any oxygen atom (single, double or triple bonded) by 5 bond distance in a molecule. These findings were supported by the compounds **22**, **23**, **24**, **25**, **26** and **27** which have substitution of 2-OPh-Ph, 3-OPh-Ph, 4-OPh-Ph, 2-O-nBu-Ph, 2,4-(O-*n*Pr)$_2$-Ph or 2,4-(O-*n*Bu)$_2$-Ph at C-4 position (R_2) of imidazole. The other descriptor SlogP signifies log of the octanol/water partition coefficient (Including implicit hydrogen). The positive contribution SlogP suggests that the antidiabetic activity is increased with substitution of strong hydrophobic groups. These findings were supported by the compounds **18 to 27** which have substitution of strong hydrophobic groups specifically at C-4 position of imidazole (R_2). Modification of the parameters T_N_O_5 and SlogP for the present series of compounds will lead to good effect on antidiabetic activity.

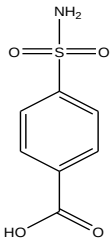
Series II: Aromatic sulfonamides

The carbonic anhydrase II inhibitory activity and structure of 47 compounds (Table 3) were used for the present study [15-17]. Different feature selection and model development methods were used to develop 2D QSAR models. One of the best developed models was Eq. (2). The criteria's used to get this model were: random training and test set selection method (80%), stepwise forward-backward variable selection method, model development by multiple linear regression (MLR), and test set compounds: **2**, **12**, **15**, **19**, **21**, **23**, **25**, **28**, **36**, **45.**

pKi = -0.605 + 0.001 (±0.000) Mol.Wt. + 0.2446 (±0.126) SsBrE-index Eq. (2)

n = 37, r^2 = 0.663, r^2se = 0.085, q^2 = 0.623, q^2se = 0.089, $F_{2,34}$ = 33.375, pred_r^2 = 0.714, pred_r^2se = 0.079, Z Score r^2 = 13.021, Z Score q^2 = 5.647, Best Rand r^2 = 0.201, Best Rand q^2 = 0.082

Table 3. The structures of para-substituted aromatic sulfonamides with their carbonic anhydrase II inhibitory activity



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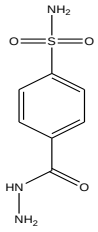

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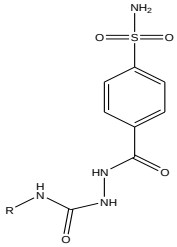
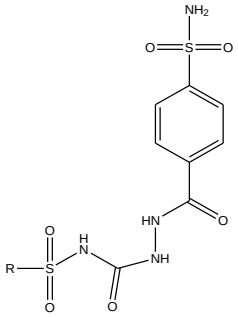


3-9

Compounds	R	pK_i
1	-	-0.382
2	-	-0.321
3	3,4-$Cl_2C_6H_3$	-0.047
4	4-Ac- C_6H_4	-0.070
5	4-EtOOC-C_6H_4	0.020
6	4-Br-C_6H_4	0.064
7	4-Ph-C_6H_4	-0.018
8	4-PhO-C_6H_4	-0.099
9	4-$PhCH_2$-C_6H_4	-0.070



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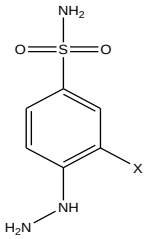

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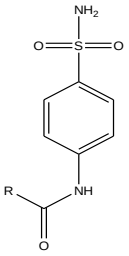
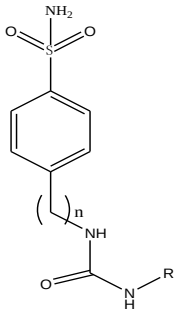


17-26

Compounds	R	pK_i
10	Ph	-0.102
11	2-Me-C_6H_4	-0.084
12	4-Me-C_6H_4	-0.084
13	4-F-C_6H_4	-0.079
14	4-Cl-C_6H_4	-0.059
15	X = F	-0.346
16	X = Cl	-0.325
17	Me	-0.334
18	CF_3	-0.266
19	Et	-0.317
20	*n*-Pr	-0.281
21	*i*-Pr	-0.299
22	*n*-Bu	-0.264
23	*t*-Bu	-0.264
24	n-C_5H_{11}	-0.264
25	Ph	-0.264
26	C_6F_5	-0.143



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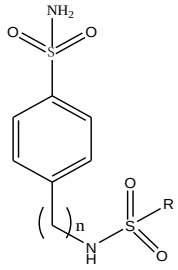
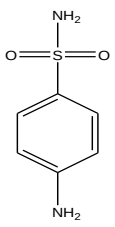


31-35

Compounds	n	R	pK_i
27	0	Ph	-0.237
28	1	Ph	-0.219
29	2	Ph	-0.202
30	2	3,4-$Cl_2C_6H_3$	-0.115
31	0	Ph	-0.211
32	1	Ph	-0.193
33	2	Ph	-0.175
34	0	4-FC_6H_4	-0.188
35	2	4-$AcNHC_6H_4$	-0.103



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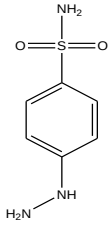

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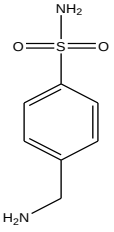

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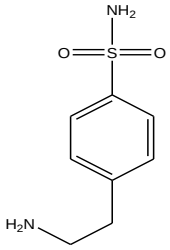

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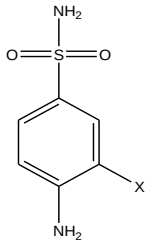
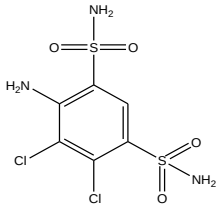


40-43

Compounds	X	pK_i
36	-	-0.387
37	-	-0.369
38	-	-0.370
39	-	-0.352
40	F	-0.365
41	Cl	-0.344
42	Br	-0.194
43	I	-0.229



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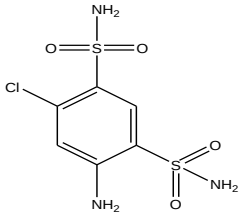

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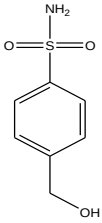

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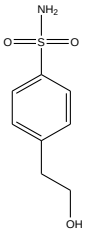

47

Compounds	R	pK_i
44	-	-0.201
45	-	-0.244
46	-	-0.369
47	-	-0.351

Table 4. Descriptors involved in 2D QSAR model Eq. (2) for para-substituted aromatic sulfonamides as carbonic anhydrase II inhibitors with their actual and predicted activities

Compounds	Molecular weight	SsBrE-index	Actual activity (pK_i)	Predicted activity (pK_i)
1	201.203	0	-0.382	-0.382
2[a]	215.233	0	-0.321	-0.321
3	403.245	0	-0.047	-0.047
4	376.393	0	-0.070	-0.07
5	408.435	0	0.020	0.02
6	413.252	0.573	0.064	0.064
7	410.453	0	-0.018	-0.018
8	426.453	0	-0.099	-0.099
9	426.496	0	-0.070	-0.07
10	398.421	0	-0.102	-0.262
11	412.447	0	-0.084	-0.239
12[a]	412.447	0	-0.084	0.004
13	416.411	0	-0.079	0.01
14	432.865	0	-0.059	0.018
15[a]	205.213	0	-0.346	-0.232
16	221.667	0	-0.325	-0.274
17	214.245	0	-0.334	-0.379
18	268.216	0	-0.266	-0.327
19[a]	228.272	0	-0.317	-0.374
20	256.326	0	-0.281	-0.372
21[a]	242.299	0	-0.299	-0.382
22	270.353	0	-0.264	-0.367

Compounds	Molecular weight	SsBrE-index	Actual activity (pK_i)	Predicted activity (pK_i)
23[a]	270.353	0	-0.264	-0.373
24	270.353	0	-0.264	-0.255
25[a]	270.353	0	-0.264	-0.195
26	366.268	0	-0.143	-0.09
27	291.331	0	-0.237	-0.377
28[a]	305.358	0	-0.219	-0.306
29	319.384	0	-0.202	-0.273
30	388.274	0	-0.115	-0.047
31	312.37	0	-0.211	-0.228
32	326.397	0	-0.193	-0.205
33	340.424	0	-0.175	-0.161
34	330.361	0	-0.188	0.02
35	397.476	0	-0.103	-0.273
36[a]	172.208	0	-0.387	-0.394
37	187.222	0	-0.369	-0.399
38	186.235	0	-0.370	-0.348
39	200.262	0	-0.352	-0.343
40	190.198	0	-0.365	-0.25
41	206.653	0	-0.344	-0.31
42	251.104	0.383	-0.194	-0.205
43	298.108	0	-0.229	-0.266
44	320.177	0	-0.201	-0.161
45[a]	285.732	0	-0.244	-0.273
46	187.219	0	-0.369	-0.322
47	201.246	0	-0.351	-0.31

[a] – indicates test set compound

Eq. (2) could explain 66.3% and predict 71.4% of the variance of the carbonic anhydrase II inhibitory activity data. There was no inter-correlation between the descriptors. The parameters involved in the selected model (Molecular weight and SsBrE-index) and the calculated antidiabetic activity by Eq. (2) are given in Table 4.

The correlation of experimental activity against predicted activities by Eq. (2) is graphically represented in Figure 4. The closeness of the actual and predicted activity by Eq. (2) for training and test set compounds are shown in Figure 5 and 6, respectively. The selected model was good in internal prediction (q^2 = 0.846) and external prediction (pred_r^2 = 0.714). The good results in our original model are not due to a chance correlation or structural dependency of the compounds was buttressed by the low randomized r^2 (0.201) and q^2 (0.082) values.

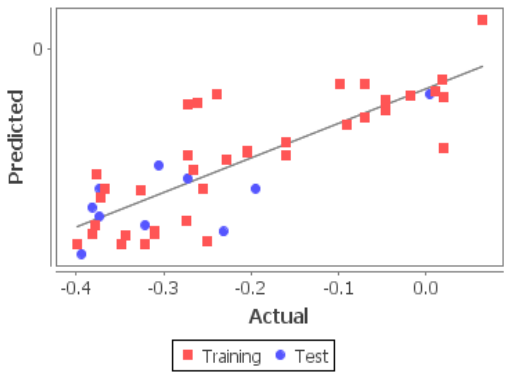

Figure 4. Fitness plot between the experimental and predicted activities by Eq. (2)

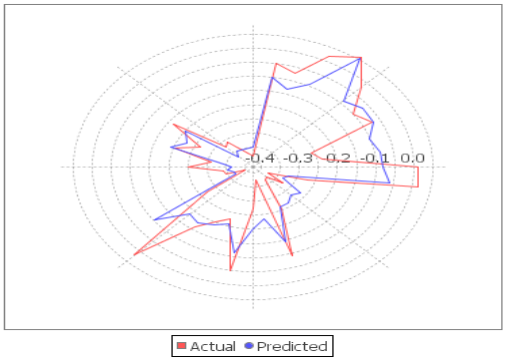

Figure 5. Radar plot depicting closeness between the actual and predicted activity of training set compounds by Eq. (2)

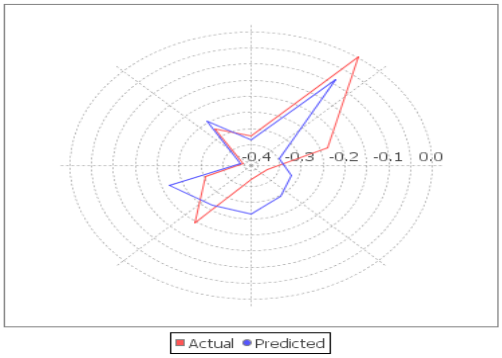

Figure 6. Radar plot depicting closeness between the actual and predicted activity of test set compounds by Eq. (2)

The developed MLR model reveals that the descriptor molecular weight showed positive contribution. Such positive effect indicates that the antidiabetic activity is increased with substitution of bulky groups in the compounds. These findings were supported by the compounds **5**, **6**, **12**, **13** and **14** which have high molecular weight. The other descriptor, SsBrE-index is an electrotopological indices descriptor influencing

activity variation and is directly contributing to activity. This descriptor reveals the importance of presence of number of bromine atom connected with one single bond in the compounds. Carbonic anhydrase II inhibitory activity of sulfonamides is increased with substitution of more bromine. Modification of the parameters molecular weight and SsBrE-index in the present series of sulfonamide compounds will lead to good effect on antidiabetic activity.

4. Conclusion

In the present study, statistically significant and highly predictive 2D QSAR models were developed for some antidiabetic compounds. The QSAR models were validated by standard statistical measures, cross-validated correlation coefficient, external test set and randomization test, and through observation on how it reproduces and explains the quantitative differences seen in the experimentally known activity data. The models are considered predictive model as the validation methods provided significant statistical parameters with $q^2 = 0.880, 0.623$ and pred_$r^2 = 0.830, 0.714$, respectively for model 1 and 2. The developed 2D QSAR models revealed the importance of SlogP, T_N_O_5, Mol.Wt and SsBrE-index properties of compounds in their antidiabetic activity. These results will be an essential guide for the further design and development of new lead compounds of more potent antidiabetic compounds.

These studies can be further extended to develop QSAR models using some other approaches HQSAR, PARM, 3D QSAR and docking analysis of direct drug designing and further validation of the results obtained in the present studies. The field is further open for designing, synthesis and biological evaluation of potent antidiabetic compounds, pharmacokinetic studies and clinical studies to establish those molecules as drug.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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