Available online on 15.03.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Identification of Some α-Glucosidase Inhibitors Using QSAR Modeling Based Drug Repurposing Approach

Sonu [1], Mohan Lal Kori [2]*

[1] Ph. D. Research scholar RKDF University Bhopal (M.P.), India

[2] Vice Chancellor, Tantya Bhil University Khargone (M.P.), India

Article Info:

Article History:

Received 17 Dec 2024
Reviewed 26 Jan 2025
Accepted 20 Feb 2025
Published 15 March 2025

Cite this article as:

Sonu, Kori ML, Identification of Some α-Glucosidase Inhibitors Using QSAR Modeling Based Drug Repurposing Approach, Journal of Drug Delivery and Therapeutics. 2025; 15(3):36-52 *DOI: http://dx.doi.org/10.22270/jddt.v15i3.7029*

*Address for Correspondence:

Mohan Lal Kori, Vice Chancellor, Tantya Bhil University Khargone (M.P.), India

Abstract

Post-prandial hyperglycemia still remains a problem in the management of type II diabetes mellitus. Of all available anti-diabetic drugs, α-glucosidase inhibitors seem to be one of the most effective in reducing post-prandial hyperglycemia. In present study, QSAR modeling based drug repurposing approach has been implemented to identify some repurposed α-glucosidase inhibitors with established safety profile. For this QSAR modeling based analysis, initially a series of N'-Benzylidenebenzoylhydrazide having two different types of substitutions on Benzylidene and Benzoyl part as well as proper variation in the biological activity was selected thereafter models were developed using various conventional QSAR approaches including Free Wilson, Hansch, and Mixed modeling by utilizing PaDEL descriptor calculator and DTC lab software. Hansch type 2D QSAR model, which was derived using some PaDEL descriptor, showed acceptable internal as well as external consistencies. Some repurposed α-glucosidase inhibitors were successfully identified. These identified approved drugs may be further explored as new anti-diabetics for type II diabetes patient especially for the management of post-prandial hyperglycemia which is a major issue in these patients.

Keywords: QSAR, Hyperglycemia, Substitutions, Diabetes mellitus, PaDEL descriptor

1. INDRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia caused by inadequate insulin secretion with or without a simultaneous decrease in hormone action at its receptor [1].

Currently, diabetes is the fifth deadliest disease. As per WHO report, about 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades [2].

Post-prandial hyperglycemia still remains a problem in the management of type 2 diabetes mellitus. Of all available anti-diabetic drugs, α-glucosidase inhibitors seem to be one of the most effective in reducing post-prandial hyperglycemia [3].

Alpha-amylase and alpha-glucosidase are the key enzymes responsible for metabolism of carbohydrates. Alpha-glucosidase Inhibitors (AGIs) are oral anti-diabetic drugs preferably for treatment of T2DM. AGIs delay the process of carbohydrate absorption in the gastrointestinal tract by moving the undigested carbohydrate into the distal part of small intestine and colon. This class of drugs helps in reduction in postprandial hyperglycaemia [4]. AGIs are saccharides that act as competitive inhibitors for the enzymes in the small intestine to slow down the digestion of carbohydrates such as starch, so that glucose from food enters the bloodstream more slowly, leading to the reduction in postprandial hyperglycaemia (**Fig.1**).

There are three FDA approved AGIs available in the market **(Fig. 2).** Acarbose obtained from Actinomyces utahensis was the first AGIs, used as a competitive inhibitor of α-glucosidase [5]. Voglibose and Miglitol are the other AGIs used for management of Type II diabetes [6]. These drugs have benefits in reducing post-prandial sugars when usually combined with other anti-diabetic drugs and thus lower HbA1c [7]. These facilitate to raise post meal levels of GLP-1 that subsequently delays digestion and decreases appetite [8].

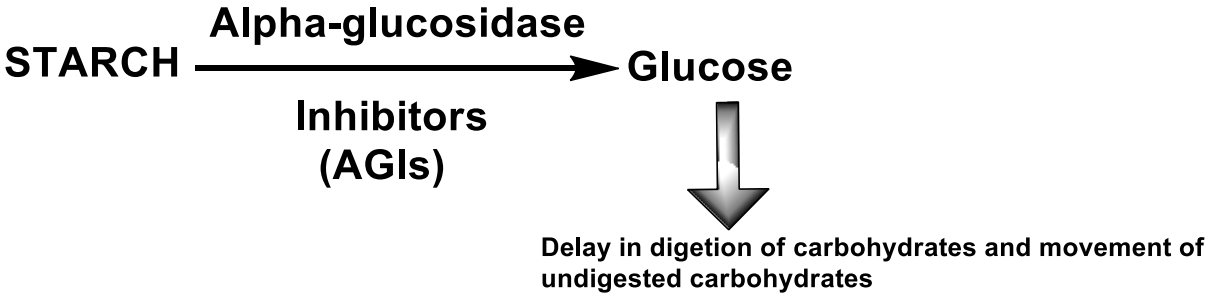


Figure 1: Mechanism of α-glucosidase inhibitors for controlling post-prandial glucose levels

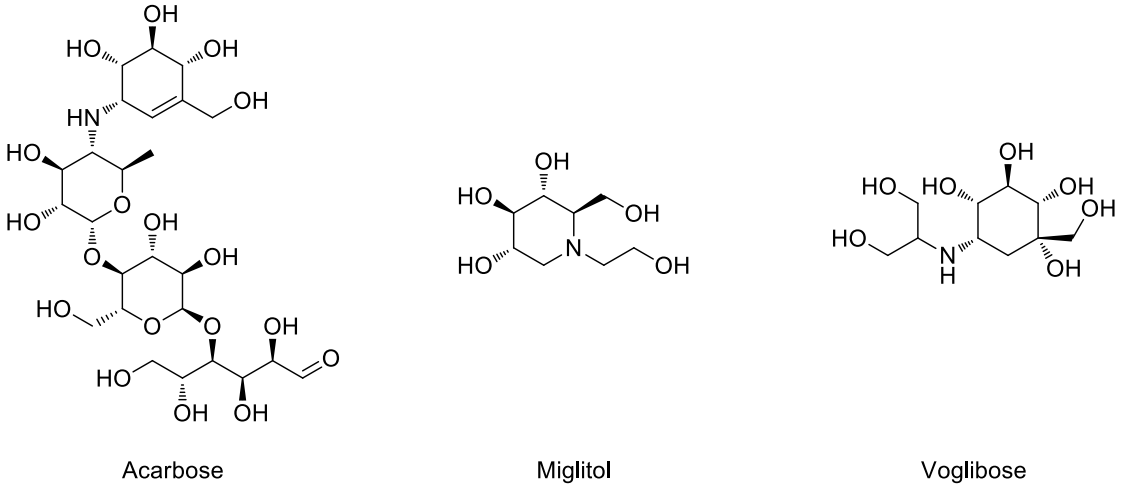


Figure 2: FDA approved α-glucosidase inhibitors

Side effects of AGIs typically include bloating, flatulence, gastrointestinal irritation that might be recovered in few weeks [9]. α-glucosidase inhibitors are not recommended if the person has any kind of GIT related disorder like ulcerative colitis or Crohn's disease, blockage in intestines, digestive disorder in intestines, diabetic ketoacidosis; a condition where body burns fat instead of carbohydrates for energy [9]. Acarbose is not recommended if the patient has an ulcer in large intestine, cirrhosis of the liver and for pregnant women [9, 10]

On the basis of these literature observations, it was thought worthwhile to identify some new α-glucosidase inhibitors with better safety profile therefore drug repurposing approach in combination with QSAR was considered to be better choice.

Drug repurposing is gaining popularity as a quick and effective method of identifying new therapeutic indications of approved drugs unrelated to their original medical intent, and is successfully moving towards the second phase of clinical trials. In this study, drug repurposing with QSAR based virtual screening was implemented for identification of some α-glucosidase inhibitors as new anti-diabetics.

To carried of QSAR modeling against this target, congeneric series of N'-Benzylidenebenzoylhydrazide [11-13] having two different types of substitutions on Benzylidene and benzoyl part as well as proper variation in the biological activity was selected on the basis the of thumb rules described by Hansch in his manual [14].

2. MATERIALS AND METHOD

QSAR analysis was carried out for α-glucosidase inhibitors using various conventional QSAR approaches including Free Wilson, Hansch, and Mixed modeling. For this purpose, various QSAR descriptors were collected from different sources like Hansch Manual, Medicinal Chemistry books etc.[14,15] Indicator variables for deriving Free Wilson approach were formulated from the various substituents present on the parent scaffold. Global properties of the molecules were calculated by PaDEL software [16]. QSAR models were derived by DTC QSAR modeling tool [17]. Internal and external validations were carried out by calculating various statistical parameters lilke Q^2, R^2_{traing}, R^2 test PRESS values etc. Virtual screening was carried out using DRUGBANK data base [18].

3. RESULTS AND DISCUSSION

For QSAR modeling, data set of N'-Benzylidenebenzoylhydrazide scaffold based α-glucosidase inhibitors containing 49 molecules was divided into training set of 35 molecules and test set of 14 molecules. Details about training set and test set are given in the **Table 1.** Training set was used for determining internal predictive ability whereas test set was used for external predictive ability of the QSAR model. Inhibitory activity data i.e. IC_{50} was collected from the literature. IC_{50} of the compounds represent

their doses in micromolar concentration (μM) required to produce 50% inhibition of α-glucosidase enzyme. The given IC_{50} data is first converted into pIC_{50} by taking negative log of IC_{50}, where IC_{50} is in molar concentration. The values of pIC_{50} of all molecules in the data set are described in **Table 1**.

3.1 Free-Wilson model

QSAR modeling was started with Free Wilson approach. For this purpose various indicator variables were recorded for different functionality at R1 by assigning value 1 for presence of the particular group and value 0 for absence of that group. Indicator values are described in **Table 2.** Free Wilson model was developed by taking pIC_{50} as dependent variable and various indicator variables as independent variables. The best model generated is given in **Equation 1.** Evaluation parameters of this model clearly indicate that Model Quality is poor and therefore this model cannot be accepted for further analysis.

pIC_{50}=4.64304(+/-0.07845)-1.45673(+/-0.31379) *R3-OCH3* -1.41197(+/-0.43677) *R2-Br* -1.33974(+/-0.43677) *R3-CH3* -1.20817(+/-0.43677) *R4-CH3*.....**1**

Descriptions about selected variables are as follows:

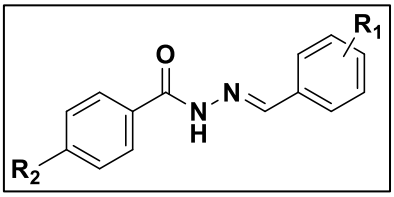
R3-OCH3 => 'Negative Contribution'

R2-Br => 'Negative Contribution'

R3-CH3 => 'Negative Contribution'

R4-CH3 => 'Negative Contribution'

Table 1: Training set and test set data for QSAR analysis of α-glucosidase inhibitors



Compound No	R_1	R_2	IC_{50} [a]	pIC_{50}[b]
1	2,4,6-OH	4*H*-chromen-4-one	15.4	4.812
2	2,3-OH	4*H*-chromen-4-one	16.9	4.772
3	2,4-OH	4*H*-chromen-4-one	27.3	4.564
4	2,5-OH	4*H*-chromen-4-one	37.8	4.423
*5	3,4-OH	4*H*-chromen-4-one	17.2	4.764
*6	2-OH	4*H*-chromen-4-one	37.4	4.427
7	3-OH	4*H*-chromen-4-one	86.3	4.064
8	4-OH	4*H*-chromen-4-one	27.4	4.562
9	2-OH, 4-OCH3	4*H*-chromen-4-one	29.4	4.532
10	3-OH, 4OCH3	4*H*-chromen-4-one	34.4	4.463
11	2-OH, 5OCH3	4*H*-chromen-4-one	37.4	4.427
12	3,5-OCH3	4*H*-chromen-4-one	623.1	3.205
13	2-Br, 4-OH	4*H*-chromen-4-one	587.4	3.231
*14	2-CH3	4*H*-chromen-4-one	487.4	3.312
15	3-CH3	4*H*-chromen-4-one	497.4	3.303
16	4-CH3	4*H*-chromen-4-one	367.4	3.435
*17	2-Cl	4*H*-chromen-4-one	29.6	4.529
18	3-Cl	4*H*-chromen-4-one	64.5	4.190
19	4-Cl	4*H*-chromen-4-one	38.3	4.417
20	2-NO2	4*H*-chromen-4-one	123.4	3.909
*21	3-NO2	4*H*-chromen-4-one	98	4.009
*22	4-NO2	4*H*-chromen-4-one	88.4	4.054

*23	2-F	4*H*-chromen-4-one	17.1	4.767
24	3-F	4*H*-chromen-4-one	22.8	4.642
25	4-F	4*H*-chromen-4-one	19.4	4.712
26	3-OCH3	4*H*-chromen-4-one	680.5	3.167
27	4-OCH3	4*H*-chromen-4-one	690.3	3.161
28	2-OH, 5OCH3	Benzo[d]thiazole	6.5	5.187
29	4-OH	Benzo[d]thiazole	11.29	4.947
30	2,3-OH	Benzo[d]thiazole	11.22	4.950
31	2-OH, 4-OCH3	Benzo[d]thiazole	6.97	5.157
*32	2-OH	Benzo[d]thiazole	5.55	5.256
33	3,4-OH	Benzo[d]thiazole	15.09	4.821
*34	2,4-OH	Benzo[d]thiazole	5.58	5.253
35	4-NO2	Benzo[d]thiazole	26.38	4.579
*36	4-F	Benzo[d]thiazole	7.12	5.148
*37	3,5-OCH3	Benzo[d]thiazole	16.17	4.791
*38	H	Benzo[d]thiazole	8.05	5.094
39	3-Br, 4-F	Benzo[d]thiazole	28.02	4.553
40	4-OCH3	Benzo[d]thiazole	18.33	4.737
41	2,4,6-OH	Benzo[d]thiazole	8.37	5.077
42	3-Br, 4-OH	Benzo[d]thiazole	8.07	5.093
43	4-Cl	Benzo[d]thiazole	5.31	5.275
*44	3-OCH3	Benzo[d]thiazole	11.09	4.955
45	3-OH	Benzo[d]thiazole	9.21	5.036
*46	3-OCH3,4-OH	Benzo[d]thiazole	53.34	4.273
47	2-I,3-OH,4-OCH3	Benzo[d]thiazole	44.8	4.349
48	2,5-OH	Benzo[d]thiazole	11.85	4.926
49	3,5-OH	Benzo[d]thiazole	11.12	4.954

* Test set compounds, [a] Dose in micromolar concentration required to produce 50% inhibition of α-glucosidase, [b] $-\log IC_{50}$

Total number of compounds: 49

Number of trainings: 35, number of tests: 14

Internal Validation Parameters:

SEE :0.4296, **r^2** :0.5951, **r^2 adjusted** :0.541, **PRESS** :5.5384, **F** :11.0264 (DF :4, 30)

Leave-One-Out(LOO) Result :

Q2 :0.2954

Rm^2metrics (after scaling the data): **Average rm^2(LOO)**:0.15569, **Delta rm^2(LOO)**:0.28955

External Validation Parameters (Without Scaling):

r^2 :0.03782, **r0^2** :-1.3350, **reverse r0^2**:-1.4060, **RMSEP**:0.8305, **Q2f1/R^2(Pred)** :-1.1619, **Q2f2** :-1.37693

External Validation Parameters (After Scaling):

Average rm^2(test) :-0.00375, Delta rm^2(test) :0.00595

Error Based Judgement of Test Set Predictions:

Mean Absolute Error (MAE; 95% data): 0.56031

Standard Deviation of Absolute Error (SD; 95% data): 0.4517

Model Quality based on MAE-based criteria: 'BAD'

Golbraikh and Tropsha acceptable model criteria's[19]:

1. **Q^2** 0.2954 **Failed*** (Threshold value Q^2>0.5)

2. **r^2** 0.0378 **Failed*** (Threshold value r^2>0.6)

3. **|r0^2-r'0^2|**0.0709 **Passed** (Threshold value |r0^2-r'0^2|<0.3)

4. **k** 1.0247**[(r^2-r0^2)/r^2]** 36.3040, OR***k'**0.9452 **[(r^2-r'0^2)/r^2]** 8.1813 **Failed***

Table 2: Indicator variables of Training set and test set molecules of α-glucosidase inhibitors for Free Wilson model

S. N.	pIC50	R2-OH	R3-OH	R4-OH	R5-OH	R6-OH	R2-OCH3	R3-OCH3	R4-OCH3	R5-OCH3	R6-OCH3	R2-CH3	R3-CH3	R4-CH3	R2-Cl
1	4.812	1	0	1	0	1	0	0	0	0	0	0	0	0	0
2	4.772	1	1	0	0	0	0	0	0	0	0	0	0	0	0
3	4.564	1	0	1	0	0	0	0	0	0	0	0	0	0	0
4	4.423	1	0	0	1	0	0	0	0	0	0	0	0	0	0
5	4.764	0	1	1	0	0	0	0	0	0	0	0	0	0	0
6	4.427	1	0	0	0	0	0	0	0	0	0	0	0	0	0
7	4.064	0	1	0	0	0	0	0	0	0	0	0	0	0	0
8	4.562	0	0	1	0	0	0	0	0	0	0	0	0	0	0
9	4.532	1	0	0	0	0	0	0	1	0	0	0	0	0	0
10	4.463	0	1	0	0	0	0	0	1	0	0	0	0	0	0
11	4.427	1	0	0	0	0	0	0	0	1	0	0	0	0	0
12	3.205	0	0	0	0	0	0	1	0	1	0	0	0	0	0
13	3.231	0	0	1	0	0	0	0	0	0	0	0	0	0	0
14	3.312	0	0	0	0	0	0	0	0	0	0	1	0	0	0
15	3.303	0	0	0	0	0	0	0	0	0	0	0	1	0	0
16	3.435	0	0	0	0	0	0	0	0	0	0	0	0	1	0
17	4.529	0	0	0	0	0	0	0	0	0	0	0	0	0	1
18	4.190	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	4.417	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	3.909	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	4.009	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	4.054	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	4.767	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	4.642	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Conti....

S.no	R3-Cl	R4-Cl	R2-NO2	R3-NO2	R4-NO2	R2-F	R3-F	R4-F	R1-H	R2-H	R3-H	R4-H	R5-H	R6-H	R2-Br	R3-Br
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0

Conti…….

S. N.	pIC50	R2-OH	R3-OH	R4-OH	R5-OH	R6-OH	R2-OCH3	R3-OCH3	R4-OCH3	R5-OCH3	R6-OCH3	R2-CH3	R3-CH3	R4-CH3	R2-Cl
25	4.712	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	3.167	0	0	0	0	0	0	1	0	0	0	0	0	0	0
27	3.161	0	0	0	0	0	0	0	1	0	0	0	0	0	0
28	5.187	1	0	0	0	0	0	0	0	1	0	0	0	0	0
29	4.947	0	0	1	0	0	0	0	0	0	0	0	0	0	0
30	4.950	1	1	0	0	0	0	0	0	0	0	0	0	0	0
31	5.157	1	0	0	0	0	0	0	1	0	0	0	0	0	0
32	5.256	1	0	0	0	0	0	0	0	0	0	0	0	0	0
33	4.821	0	1	1	0	0	0	0	0	0	0	0	0	0	0
34	5.253	1	0	1	0	0	0	0	0	0	0	0	0	0	0
35	4.579	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	5.148	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	4.791	0	0	0	0	0	0	1	0	1	0	0	0	0	0
38	5.094	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	4.553	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	4.737	0	0	0	0	0	0	0	1	0	0	0	0	0	0
41	5.077	1	0	1	0	1	0	0	0	0	0	0	0	0	0
42	5.093	0	0	1	0	0	0	0	0	0	0	0	0	0	0
43	5.275	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	4.955	0	0	0	0	0	0	1	0	0	0	0	0	0	0
45	5.036	0	1	0	0	0	0	0	0	0	0	0	0	0	0
46	4.273	0	0	1	0	0	0	0	0	0	0	0	0	0	0
47	4.349	0	1	0	0	0	0	0	1	0	0	0	0	0	0
48	4.926	1	0	0	1	0	0	0	0	0	0	0	0	0	0
49	4.954	0	1	0	1	0	0	0	0	0	0	0	0	0	0

Conti…

S. N.	R3-Cl	R4-Cl	R2-NO2	R3-NO2	R4-NO2	R2-F	R3-F	R4-F	R1-H	R2-H	R3-H	R4-H	R5-H	R6-H	R2-Br	R3-Br
25	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0
39	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 3: Substituent constants for Hansch Model

S. N.	pIC 50	R2-Pi	R3-Pi	R4-Pi	R5-Pi	R6-Pi	Total-Pi	R2-MR	R3-MR	R4-MR	R5-MR	R6-MR	Total MR	R2-L	R3-L	R4-L	R5-L	R6-L	Total-L	R2-B1
1	4.812	-0.67	0	-0.67	0	-0.67	-1.34	0.29	0	0.29	0	0.29	0.58	2.74	0	2.74	0	2.74	8.22	1.35
2	4.772	-0.67	-0.67	0	0	0	-1.34	0.29	0.29	0	0	0	0.58	2.74	2.74	0	0	0	5.48	1.35
3	4.564	-0.67	0	-0.67	0	0	-1.34	0.29	0	0.29	0	0	0.58	2.74	0	2.74	0	0	5.48	1.35
4	4.423	-0.67	0	0	-0.67	0	-1.34	0.29	0	0	0.29	0	0.58	2.74	0	0	2.74	0	5.48	1.35
5	4.764	0	-0.67	-0.67	0	0	-1.34	0	0.29	0.29	0	0	0.58	0	2.74	2.74	0	0	5.48	0
6	4.427	-0.67	0	0	0	0	-0.67	0.29	0	0	0	0	0.29	2.74	0	0	0	0	2.74	1.35

7	4.064	0	-0.67	0	0	0	-0.67	0	0.29	0	0	0	0.29	0	2.74	0	0	0	2.74	0
8	4.562	0	0	-0.67		0	-0.67	0	0	0.29	0	0	0.29	0	0	2.74	0	0	2.74	0
9	4.532	-0.67	0	-0.02	0	0	-0.69	0.29	0	0.79	0	0	1.08	2.74	0	3.98	0	0	6.72	1.35
10	4.463	0	-0.67	-0.02	0	0	-0.69	0	0.29	0.79	0	0	1.08	0	2.74	3.98	0	0	6.72	0
11	4.427	0	0	-0.67	-0.02	0	-0.69	2.09	0	0	0.79	0	2.88	2.74	0	0	3.98	0	6.72	1.35
12	3.205	0	-0.02	0	-0.02	0	-0.04	0	0.79	0	0.79	0	1.58	0	3.98	0	3.98	0	7.96	0
13	3.231	0.86	0	-0.67	0	0	0.19	0.89	0	0.29	0	0	1.18	3.82	0	2.74	0	0	6.56	1.95
14	3.312	0.56	0	0	0	0	0.56	0.57	0	0	0	0	0.57	2.87	0	0	0	0	2.87	1.52
15	3.303	0	0.56	0	0	0	0.56	0	0.57	0	0	0	0.57	0	2.87	0	0	0	2.87	0
16	3.435	0	0	0.56	0	0	0.56	0	0	0.57	0	0	0.57	0	0	2.87	0	0	2.87	0
17	4.529	0.71	0	0	0	0	0.71	0.6	0	0	0	0	0.6	3.52	0	0	0	0	3.52	1.8
18	4.190	0	0.71	0	0	0	0.71	0	0.6	0	0	0	0.6	0	3.52	0	0	0	3.52	0
19	4.417	0	0	0.71	0	0	0.71	0	0	0.6	0	0	0.6	0	0	3.52	0	0	3.52	0
20	3.909	-0.28	0	0	0	0	-0.28	0.74	0	0	0	0	0.74	3.44	0	0	0	0	3.44	1.7
21	4.009	0	-0.28	0	0	0	-0.28	0	0.74	0	0	0	0.74	0	3.44	0	0	0	3.44	0
22	4.054	0	0	-0.28	0	0	-0.28	0	0	0.74	0	0	0.74	0	0	3.44	0	0	3.44	0
23	4.767	0.14	0	0	0	0	0.14	0.09	0	0	0	0	0.09	2.65	0	0	0	0	2.65	1.35
24	4.642	0	0.14	0	0	0	0.14	0	0.09	0	0	0	0.09	0	2.65	0	0	0	2.65	0

Conti....

S.No.	R3-B1	R4-B1	R5-B1	R6-B1	Total-B1	R2-B5	R3-B5	R4-B5	R5-B5	R6-B5	Total-B5	Sp	R3-Sm	R5-Sm	Total-Sm	Combined Smp
1	0	1.35	0	1.35	4.05	1.93	0	1.93	0	1.93	5.79	-0.37	0	0	0	-0.37
2	1.35	0	0	0	2.7	1.93	1.93	0	0	0	3.86	0	0.12	0	0.12	0.12
3	0	1.35	0	0	2.7	1.93	0	1.93	0	0	3.86	-0.37	0	0	0	-0.37
4	0	0	1.35	0	2.7	1.93	0	0	1.93	0	3.86	0	0.12	0	0.12	0.12
5	1.35	1.35	0	0	2.7	0	1.93	1.93	0	0	3.86	-0.37	0.12	0	0.12	-0.25
6	0	0	0	0	1.35	1.93	0	0	0	0	1.93	0	0	0	0	0

7	1.35	0	0	0	1.35	0	1.93	0	0	0	1.93	0	0.12	0	0.12	0.12
8	0	1.35	0	0	1.35	0	0	1.93	0	0	1.93	-0.37	0	0	0	-0.37
9	0	1.35	0	0	2.7	1.93	0	3.07	0	0	5	-0.27	0	0	0	-0.27
10	1.35	1.35	0	0	2.7	0	1.93	3.07	0	0	5	-0.27	0.12	0	0.12	-0.15
11	0	0	1.35	0	2.7	1.93	0	0	3.07	0	5	0	0	0.12	0.12	0.12
12	1.35	0	1.35	0	2.7	0	3.07	0	3.07	0	6.14	0	0.12	0.12	0.24	0.24
13	0	1.35	0	0	3.3	1.95	0	1.93	0	0	3.88	-0.37	0	0	0	-0.37
14	0	0	0	0	1.52	2.04	0	0	0	0	2.04	0	0	0	0	0
15	1.52	0	0	0	1.52	0	2.04	0	0	0	2.04	0	0.83	0	0.83	0.83
16	0	1.52	0	0	1.52	0	0	2.04	0	0	2.04	0.96	0	0	0	0.96
17	0	0	0	0	1.8	1.8	0	0	0	0	1.8	0	0	0	0	0
18	1.8	0	0	0	1.8	0	1.8	0	0	0	1.8	0	0.38	0	0.38	0.38
19	0	1.8	0	0	1.8	0	0	1.8	0	0	1.8	0.53	0	0	0	0.53
20	0	0	0	0	1.7	2.44	0	0	0	0	2.44	0	0	0	0	0
21	1.7	0	0	0	1.7	0	2.44	0	0	0	2.44	0	0.71	0	0.71	0.71
22	0	1.7	0	0	1.7	0	0	2.44	0	0	2.44	0.78	0	0	0	0.78
23	0	0	0	0	1.35	1.35	0	0	0	0	1.35	0	0	0	0	0
24	1.35	0	0	0	1.35	0	1.35	0	0	0	1.35	0	0.34	0	0.34	0.34

Conti..

S. no	pIC 50	R2-Pi	R3-Pi	R4-Pi	R5-Pi	R6-Pi	Total-Pi	R2-MR	R3-MR	R4-MR	R5-MR	R6-MR	Total MR	R2-L	R3-L	R4-L	R5-L	R6-L	Total-L	R2-B1
25	4.712	0	0	0.14	0	0	0.14	0	0	0.09	0	0	0.09	0	0	2.65	0	0	2.65	0
26	3.167	0	-0.02	0	0	0	-0.02	0	0.79	0	0	0	0.79	0	3.98	0	0	0	3.98	0
27	3.161	0	0	-0.02	0	0	-0.02	0	0	0.79	0	0	0.79	0	0	3.98	0	0	3.98	0
28	5.187	-0.67	0	0	-0.02	0	-0.69	0.29	0	0	0.79	0	1.08	2.74	0	0	3.98	0	6.72	1.35
29	4.947	0	0	-0.67	0	0	-0.67	0	0	0.29	0	0	0.29	0	0	2.74	0	0	2.74	0
30	4.950	-0.67	-0.67	0	0	0	-1.34	0.29	0.29	0	0	0	0.58	2.74	2.74	0	0	0	5.48	1.35
31	5.157	-0.67	0	-0.02	0	0	-0.69	0.29	0	0.79	0	0	1.08	2.74	0	3.98	0	0	6.72	1.35
32	5.256	-0.67	0	0	0	0	-0.67	0.29	0	0	0	0	0.29	2.74	0	0	0	0	2.74	1.35
33	4.821	0	-0.67	-0.67	0	0	-1.34	0	0.29	0.29	0	0	0.58	0	2.74	2.74	0	0	5.48	0
34	5.253	-0.67	0	-0.67	0	0	-1.34	0.29	0	0.29	0	0	0.58	2.74	0	2.74	0	0	5.48	0
35	4.5	0	0	-0.2	0	0	-0.28	0	0	0.74	0	0	0.74	0	0	3.4	0	0	3.44	0

	79			8												4				
36	5.148	0	0	0.14	0	0	0.14	0	0	0.09	0	0	0.09	0	0	0	2.65	0	2.65	0
37	4.791	0	-0.02	0	-0.02	0	-0.04	0	0.79	0	0.79	0	1.58	0	3.98	0	3.98	0	7.96	0
38	5.094	0	0	0	0	0	0	0.1	0.1	0.1	0.1	0.1	0.4	2.06	2.06	2.06	2.06	2.06	10.3	1
39	4.553	0	0.86	0.14	0	0	1	0	0.89	0.09	0	0	0.98	0	3.82	2.65	0	0	6.47	0
40	4.737	0	0	-0.02	0	0	-0.02	0	0	0.79	0	0	0.79	0	0	3.98	0	0	3.98	0
41	5.077	-0.67	0	-0.67	0	-0.67	-1.34	0.29	0	0.29	0	0.29	0.58	2.74	0	2.74	0	0	5.48	1.35
42	5.093	0	0.86	-0.67	0	0	0.19	0	0.89	0.29	0	0	1.18	0	3.82	2.74	0	0	6.56	0
43	5.275	0	0	0.71	0	0	0.71	0	0	0.6	0	0	0.6	0	0	3.52	0	0	3.52	0
44	4.955	0	-0.02	0	0	0	-0.02	0	0.79	0	0	0	0.79	0	3.98	0	0	0	3.98	0
45	5.036	0	-0.67	0	0	0	-0.67	0	0.29	0	0	0	0.29	0	2.74	0	0	0	2.74	0
46	4.273	0	-0.02	-0.67	0	0	-0.69	0	0.79	0.29	0	0	1.08	0	3.98	2.74	0	0	6.72	1.35
47	4.349	1.12	-0.67	-0.02	0	0	0.43	1.39	0.29	0.79	0	0	2.47	4.23	2.74	3.98	0	0	10.95	2.15
48	4.926	-0.67	-0.67	0	0	-0.67	-1.34	0.29	0	0	0.29	0	0.58	2.74	0	0	2.74	0	5.48	1.35
49	4.954	0	-0.67	0	-0.67	0	-1.34	0	0.29	0	0.29	0	0.58	0	2.74	0	2.74	0	5.48	0

Conti..

S.no	pIC50	R2-Pi	R3-Pi	R4-Pi	R5-Pi	R6-Pi	Total-Pi	R2-MR	R3-MR	R4-MR	R5-MR	R6-MR	Total MR	R2-L	R3-L	R4-L	R5-L
25	4.712	1.35	0	0	0	1.35	0	3.07	0	0	0	3.07	0	0.12	0	0.12	0.12
26	3.167	0	1.35	0	0	1.35	0	0	3.07	0	0	3.07	-0.27	0	0	0	-0.27
27	3.161	0	0	1.35	0	2.7	1.93	0	0	3.07	0	5	0	0	0.12	0.12	0.12
28	5.187	0	1.35	0	0	1.35	0	0	1.93	0	0	1.93	-0.37	0	0	0	-0.37
29	4.947	1.35	0	0	0	2.7	1.93	1.93	0	0	0	3.86	0	0.12	0	0.12	0.12
30	4.950	0	1.35	0		2.7	1.93	0	3.07	0	0	5	-0.27		0	0	-0.27
31	5.157	0	0	0	0	1.35	1.93	0	0	0	0	1.93	0	0	0	0	0
32	5.25	1.35	1.35	0	0	2.7	0	1.93	1.93	0	0	3.86	-0.27	0.1	0	0.1	-0.1

	6													2		2	5
33	4.821	1.35	1.35	0	0	2.7	1.93	0	1.93	0	0	3.86	0	0.12	0	0.12	0.12
34	5.253	0	1.7	0	0	1.7	0	0	2.44	0	0	2.44	2.44	0.78	0	0.78	3.22
35	4.579	0	1.35	0	0	1.35	0	0	1.35	0	0	1.35	1.35	0.06	0	0.06	1.41
36	5.148	1.35	0	1.35	0	2.7	0	3.07	0	3.07	0	6.14	-0.27	0	0.12	0.12	-0.15
37	4.791	1	1	1	1	5	1	1	1	1	1	5	0	0	0	0	0
38	5.094	1.95	1.35	0	0	3.3	0	1.95	1.35	0	0	3.3	1.35		0	0	1.35
39	4.553	0	1.35	0	0	1.35	0	0	3.07	0	0	3.07	-0.27	0	0	0	-0.27
40	4.737	0	1.35	0	1.35	4.05	1.35	0	1.35	0	1.35	4.05	1.93	-0.37	0	-0.37	1.56
41	5.077	1.95	1.35	0	0	3.3	0	1.95	1.35	0	0	3.3	-0.37		0	0	-0.37
42	5.093	0	1.8	0	0	1.8	0	0	1.8	0	0	1.8	0.53	0	0	0	0.53
43	5.275	1.35	0	0	0	1.35	0	3.07	0	0	0	3.07	0	0.12	0	0.12	0.12
44	4.955	1.35	0	0	0	1.35	0	1.93	0	0	0	1.93	0	0.12	0	0.12	0.12
45	5.036	1.35	0	0	0	2.7	0	3.07	1.35	0	0	4.42	-0.37		0	0	-0.37
46	4.273	1.35	1.35	0	0	4.85	2.15	1.93	3.07	0	0	7.15	-0.27		0	0	-0.27
47	4.349	0	0	1.35	0	2.7	1.93	0	0	1.93	0	3.86	0	0.12	0.12	0.24	0.24
48	4.926	1.35	0	1.35	0	2.7	0	1.93	0	1.93	0	3.86	0	0.12	0.12	0.24	0.24
49	4.954	1.35	0	1.35	0	2.7	0	1.93	0	1.93	0	3.86	0	0.12	0.12	0.24	0.24

3.2 Hansch Model

Data was further subjected to Hansch QSAR analysis by considering substituent's constants. The values of various substituent's constants were collected from Hansch QSAR manual [14] and given in the **Table 3**. Hansch model was developed by considering pIC_{50} as dependent variable and substituent's constants of R_1 as independent variables. No model was satisfied the acceptable statistical criterion.

3.3 Mixed Model

Since no significant model was obtained from Hansch analysis, further attempt was made to develop mixed model by combining indicator variables and substituent's constants in regression analysis. 'Mixed Model' was developed by considering pIC_{50} as dependent variables and indicator variable and substituent's constants simultaneously (given in **Table 2 & 3)** as independent variables. The best 'Mixed model' is given in **Equation 2**.

pIC_{50} = 4.69764(+/-0.09082) -1.32531(+/-0.4518) *R2-Br* -1.51164(+/-0.31728) *R3-OCH3* -1.39464(+/-0.43941) *R3-CH3* -1.26264(+/-0.43941) *R4-CH3* -0.50764(+/-0.43941) *R3-Cl* -0.15881(+/-0.17639) *R2-MR*…… **2**

Description about selected variables are as follows:

R2-Br => 'Negative Contribution'

R3-OCH3 => 'Negative Contribution'

R3-CH3 => 'Negative Contribution'

R4-CH3 => 'Negative Contribution'

R3-Cl => 'Negative Contribution'

R2-MR => 'Negative Contribution'

Internal Validation Parameters:

SEE :0.42992, **r^2** :0.62175, **r^2 adjusted** :0.5407, **PRESS** :5.17522, **F** :7.67085 (DF :6, 28),Leave-One-Out(LOO) Result :, Q2 :0.39218, Rm^2 metrics (after scaling the data):

Average rm^2(LOO):0.19393, **Delta rm^2(LOO)**:0.37955

External Validation Parameters(Without Scaling):

r^2 :0.0327, **r0^2** :-1.3410, **reverse r0^2**:-1.3448, **RMSEP**:0.8288, **Q2f1/R^2(Pred)** :-1.1532, **Q2f2** :-1.3674,

External Validation Parameters (After Scaling):

Average rm^2(test):-0.00284, **Delta rm^2(test)**:0.0051

ERROR-BASED JUDGEMENT OF TEST SET PREDICTIONS

Mean Absolute Error (MAE; 95% data): 0.5518**,**

Standard Deviation of Absolute Error (SD; 95% data): 0.4592,

Model Quality based on MAE-based criteria: **'BAD'**

Statistical parameters of Mixed Model (**Equation 2**) demonstrated BAD Model Quality. Therefore, Hansch type QSAR model development was further tried by considering some global properties of the molecules which were calculated by PaDEL software [16].

3. 4 Hansch type Model using PaDEL descriptors

Data set was further subjected to Hansch type model development considering some global properties which were calculated by PaDEL software [16]. The best model is described in **Equation 3.**

pIC_{50} = 50.45765(+/-6.99755) -0.23993(+/-0.11028) *ETA_Alpha* -0.35794(+/-0.05332) *minHBa* -21.25182(+/-3.70923) *SpMin2_Bhs* -2.33671(+/-1.53196) *SpMin7_Bhm* -1.10024(+/-0.98223) *MATS4m* -0.0223(+/-0.01685) *minHBint8*

…… **…… 3**

ETA_Alpha(PaDEL; 2D)=> 'Negative Contribution' =>Sum of alpha values of all non-hydrogen vertices of a molecule

minHBa(PaDEL; 2D)=> 'Negative Contribution' =>Minimum E-States for (strong) Hydrogen Bond acceptors

SpMin2_Bhs => 'Negative Contribution' => smallest eigenvalue n. 2 of Burden matrix weighted by I-state

SpMin7_Bhm => 'Negative Contribution' => smallest eigenvalue n. 2 of Burden matrix weighted by mass

MATS4m(Dragon; 2D autocorrelations)=> 'Negative Contribution' =>Moran autocorrelation of lag 4 weighted by mass

minHBint8(PaDEL; 2D)=> 'Negative Contribution' =>Minimum E-State descriptors of strength for potential Hydrogen Bonds of path length 8

Table 4: Correlation matrix for QSAR model given in **Equation 3**

	ETA_Alpha	*minHBa*	*SpMin2_Bhs*	*SpMin7_Bhm*	*MATS4m*	*minHBint8*
ETA_Alpha	1.000					
minHBa	02726	1.000				
SpMin2_Bhs	-0.1801	-0.6902	1.000			
SpMin7_Bhm	0.4003	0.2478	0.0036	1.000		
MATS4m	0.2923	0.5778	-0.3145	0.1640	1.000	
minHBint8	-0.0317	-0.0780	-0.1468	-0.2012	-0.1131	1.000

Internal Validation Parameters:

SEE :0.3020, **r^2** :0.8133, **r^2 adjusted** :0.7733, **PRESS** :2.5543, **F** :20.3295 (**DF** :6, 28)

Leave-One-Out(LOO) Result :

Q2 :0.7466

Rm^2 metrics (after scaling the data):

Average rm^2(LOO):0.6604, **Delta rm^2(LOO)**:0.0768

External Validation Parameters(Without Scaling):

r^2 :0.8050, **r0^2** :0.7468, **reverse r0^2**:0.8046, **RMSEP**:0.2915, **Q2f1 or R^2(Pred)** :0.7336, **Q2f2** :0.7071

External Validation Parameters (After Scaling):

Average rm^2(test):0.6565, **Delta rm^2(test)** :0.1754

ERROR BASED JUDGEMENT OF TEST SET PREDICTIONS:

Mean Absolute Error (MAE; 95% data): 0.2047,

Standard Deviation of Absolute Error (SD; 95% data): 0.1074

Model Quality based on MAE-based criteria: **'MODERATE'**

Golbraikh and Tropsha acceptable model criteria's[19] :

1. **Q^** 0.7466 **Passed** (Threshold value Q^2>0.5)

2. **r^2** 0.8050 **Passed** (Threshold value r^2>0.6)

3. **|r0^2-r'0^2|** 0.0577 **Passed** (Threshold value |r0^2-r'0^2|<0.3)

4. **k** 1 .0236 [(r^2-r0^2)/r^2] 0.0723 OR* **k'** 0.9735 [(r^2-r'0^2)/r^2] 0.0005 **Passed**

(Threshold value: [0.85<k<1.15 and ((r^2-r0^2)/r^2)<0.1] OR* [0.85<k'<1.15 and ((r^2-r'0^2)/r^2)<0.1])

Statistical evaluation of **Equation 3** clearly demonstrated that model is having acceptable values of primary statistical parameters including SEE: 0.3020, r^2 : 0.8133, r^2 adjusted :0.7733, PRESS :2.5544, F :20.3295, Q^2 :0.7466 which determine internal consistency and **r^2** :0.8050, r_0^2 :0.7468, reverse r_0^2 : 0.8046, RMSEP:0.2915, Q^2f1 or R2(Pred) :0.7336, Q2f2 :0.7071 Average rm^2(test) :0.6565, Delta rm^2(test) :0.1754 which determine external predictive ability. Other criterion including Model Quality based on MAE-based criteria and Golbraikh and Tropsha [5] acceptable model criteria's also pass the model for its acceptability to use it for screening α-glucosidase inhibitors and prediction of their activities. Predicted activities of training and test set molecules from the best model, **Equation 3**, along with residual values are given in **Table 5.** Graph of observed vs predicted activity from this model is shown in **Fig. 2** and compound vs residual is shown in **Fig. 3.** These graphs clearly indicate that most of the compounds predicted within ± 0.5 pIC_{50} units.

Table 5: Predicted activities of training and test set molecules along with residual values

Compound No.	OBS pIC_{50}[a]	PRED. pIC_{50}[b]	RESIDUAL[c]
1	4.812	4.736	0.076
2	4.772	4.581	0.191
3	4.564	4.641	0.077
4	4.423	4.505	0.082
7	4.064	4.262	0.198
8	4.562	4.474	0.088
9	4.532	4.220	0.312
10	4.463	4.058	0.405
11	4.427	4.174	0.253
12	3.205	3.186	0.019
13	3.231	3.417	0.186
15	3.303	3.105	0.198
16	3.435	3.286	0.149
18	4.190	4.256	0.066
19	4.417	4.362	0.055
20	3.909	3.621	0.288
24	4.642	4.512	0.130
25	4.712	4.570	0.142
26	3.167	3.940	0.773
27	3.161	4.056	0.895
28	5.187	5.002	0.185
29	4.947	5.030	0.083

30	4.950	5.068	0.118
31	5.157	4.985	0.172
33	4.821	5.034	0.213
35	4.579	4.769	0.190
39	4.553	4.821	0.268
40	4.737	4.895	0.158
41	5.077	5.207	0.130
42	5.093	4.835	0.258
43	5.275	4.961	0.314
45	5.036	4.828	0.208
47	4.349	4.385	0.036
48	4.926	4.995	0.069
49	4.954	4.856	0.098
5*	4.764	4.519	0.245
6*	4.427	4.537	0.110
14*	3.312	3.097	0.215
17*	4.529	4.317	0.212
21*	4.009	3.679	0.330
22*	4.054	3.676	0.378
23*	4.767	4.624	0.143
32*	5.256	5.077	0.179
34*	5.253	5.152	0.101
36*	5.148	5.088	0.060
37*	4.791	4.397	0.394
38*	5.094	4.904	0.190
44*	4.955	4.851	0.104
46*	4.273	4.985	0.712

* Test compounds, [a] - $\log IC_{50}$, where IC_{50} is experimental reported in the literature,

[b] predicted $-\log(IC_{50})$ from the best model Equation 3, [c] $OBEpIC_{50}$-$PRED.pIC_{50}$

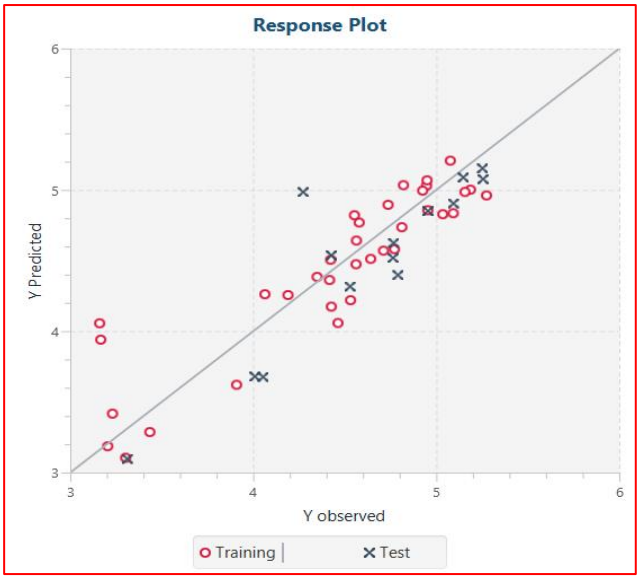


Figure 2: Graph of observed Vs. Predicted activities of training and test sets from **Equation 3**

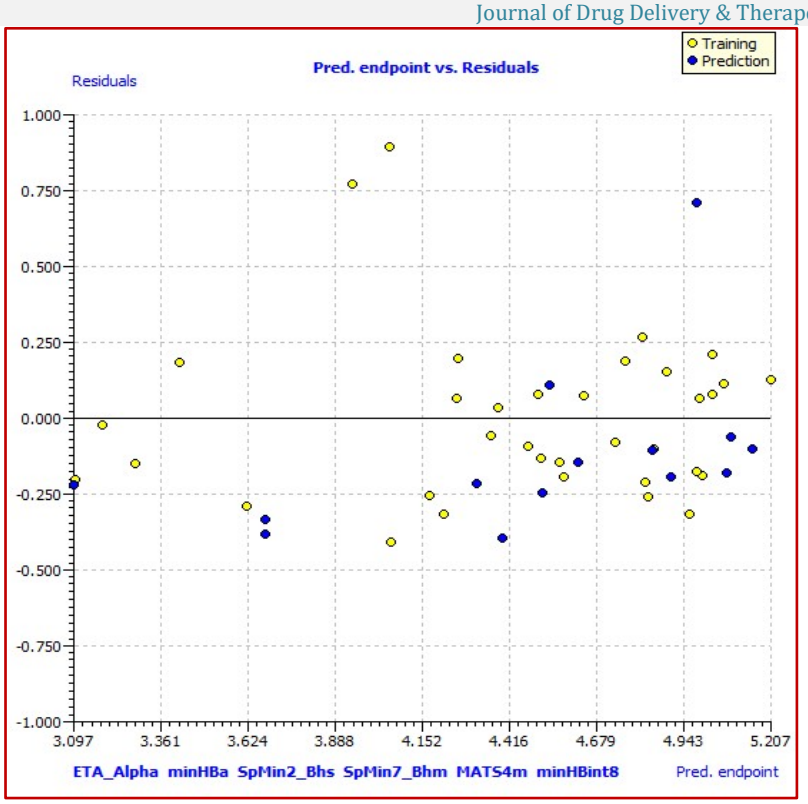


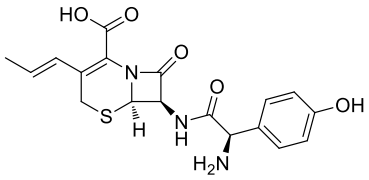
Figure 3: Resisual plot for training and test set

Some α-glucosidase inhibitors were identified by QSAR model based virtual screening (VS) protocol. VS are a computational technique used in identification new bioactive molecules. It deals with the quick search of large libraries of chemical structures in order to identify those structures which are most likely to map over the query *in silico* model. For this purpose, the best QSAR model of α-glucosidase inhibitors, given in **Equation 4.3,** was used to screen out some α-glucosidase inhibitors as NCE with anti-diabetic effect. These best models were used as filters for screening DRUGBANK using Predict Module of DTC QSAR tool [17, 18]. To predict activities of the screened out molecules, descriptors of these were calculated by PaDEL software [16]. Some identified α-glucosidase inhibitors along with their predicted in along with predicted pIC_{50} from **Equation 3** is given in **Table 6**. Top ten repurposed α-glucosidase inhibitors screened out by virtual screening using **Equation 3** as query against DRUGBANK are shown in **Fig.4.**

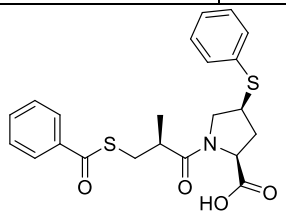
Table 6: Newly identify α-glucosidase inhibitors as anti-diabetic drug

Drug bank ID	**Predicted pIC_{50}**	AD status	**Drug Name**
DB01150	6.76	Inside-AD	Cefprozil
DB13166	6.34	Inside-AD	Zofenopril
DB00257	6.02	Inside-AD	Clotrimazole
DB00831	5.99	Inside-AD	Trifluoperazine
DB01224	5.91	Inside-AD	Quetiapine
DB04938	5.85	Inside-AD	Ospemifene
DB00623	5.81	Inside-AD	Fluphenazine
DB11952	5.81	Inside-AD	Duvelisib
DB08893	5.73	Inside-AD	Mirabegron
DB00433	5.72	Inside-AD	Prochlorperazine
DB11689	5.69	Inside-AD	Selumetinib
DB08896	5.60	Inside-AD	Regorafenib
DB12401	5.58	Inside-AD	Bromperidol
DB00850	5.56	Inside-AD	Perphenazine
DB11656	5.50	Inside-AD	Rebamipide
DB00972	5.40	Inside-AD	Azelastine

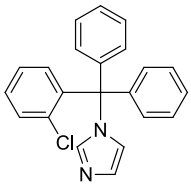
DB13248	5.39	Inside-AD	Phthalylsulfathiazole
DB00562	5.39	Inside-AD	Benzthiazide
DB06626	5.38	Inside-AD	Axitinib
DB00328	5.36	Inside-AD	Indomethacin
DB00398	5.33	Inside-AD	Sorafenib
DB06820	5.30	Inside-AD	Sulconazole
DB08976	5.29	Inside-AD	Floctafenine
DB00639	5.15	Inside-AD	Butoconazole
DB12404	5.14	Inside-AD	Remimazolam
DB15456	5.14	Inside-AD	Vericiguat
DB01608	5.11	Inside-AD	Periciazine
DB13783	4.98	Inside-AD	Acemetacin



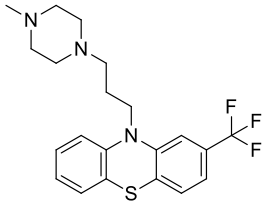
Cefprozil
(6R,7R)-7-[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]
amino]-8-oxo-3-[(E)-prop-1-enyl]
-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



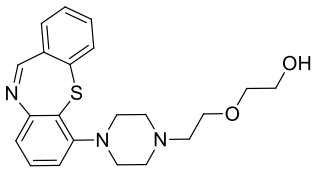
Zofenopril
(2S,4S)-1-[(2S)-3-benzoylsulfanyl-2-methylpropanoyl]
-4-phenylsulfanylpyrrolidine-2-carboxylic acid



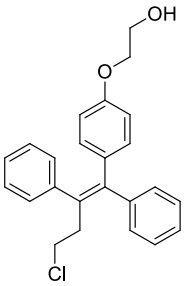
Clotrimazole
1-[(2-chlorophenyl)-diphenylmethyl]imidazole



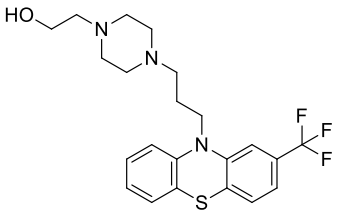
Trifluoperazine
10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)phenothiazine



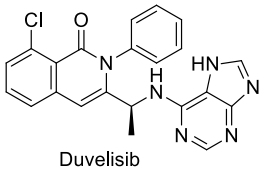
Quetiapine
2-[2-(4-benzo[b][1,4]benzothiazepin-6-ylpiperazin-1-yl)
ethoxy]ethanol



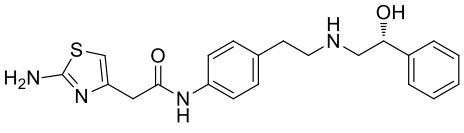
Ospemifene
2-[4-[(Z)-4-chloro-1,2-diphenylbut-1-enyl]
phenoxy]ethanol



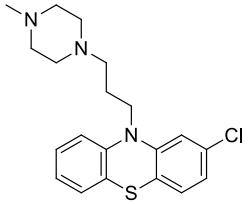
Fluphenazine
2-[4-[3-[2-(trifluoromethyl)phenothiazin-10-yl]
propyl]piperazin-1-yl]ethanol



Duvelisib
8-chloro-2-phenyl-3-[(1S)-1-(7H-purin-6-ylamino)
ethyl]isoquinolin-1-one



Mirabegron
2-(2-amino-1,3-thiazol-4-yl)-N-[4-[2-[[(2R)-2-hydroxy-2-
phenylethyl]amino]ethyl]phenyl]acetamide



Prochlorperazine
2-chloro-10-[3-(4-methylpiperazin-1-
yl)propyl]phenothiazine

Figure 4: Top ten repurposed α-glucosidase inhibitors screened out by virtual screening using **Equation 3** as query against DRUGBANK.

4. CONCLUSION

On the basis of this QSAR modeling it can conclude that a Hansch type 2D QSAR model has been successfully developed by utilizing some 2D PaDEL descriptors. Generated model was thoroughly evaluated by means of all reported statistical parameters. This validation results of the best model **Equation 3** are in acceptable criterion and therefore suggest model's reliability to be used in VS for identifying repurposed α-glucosidase inhibitors which may be further develop as new effective anti-diabetic in management of post-prandial hyperglycemia in the type II diabetes without additional safety measurement.

Acknowledgements: None

Conflict of Interest: The authors declare no potential conflict of interest with respect to the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contribution in the preparation of manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approvals: This study does not involve experiments on animals or human subjects.

REFERENCES

1. Pizzi RA. Defying diabetes: The discovery of insulin. Modern Drug Discovery 2000; 3(6):77-80.

2. APh A Special Report. New approaches to insulin therapy for diabetes. American Pharmaceutical Association, Washington DC 2001.

3. Derosa G, Maffioli P. α-Glucosidase inhibitors and their use in clinical practice, Arch Med Sci 2012; 5:899-906 https://doi.org/10.5114/aoms.2012.31621 PMid:23185202 PMCid:PMC3506243

4. Wehmeier U, Piepersberg W. Biotechnology and molecular biology of the α - glucosidase inhibitor acarbose, Appl. Microbiol. Biot. 2004; 63:613-625. https://doi.org/10.1007/s00253-003-1477-2 PMid:14669056

5. Narita T, Yokoyama H, Yamashita R, Sato T, Hosoba M, Morii T., et al., Comparisons of the effects of 12-week administration of miglitol and voglibose on the responses of plasma incretins after a mixed meal in Japanese type 2 diabetic patients, Diabetes. Obes. Metab. 2011; 14:283-287. https://doi.org/10.1111/j.1463-1326.2011.01526.x PMid:22051162

6. Derosa G, Mereu R, D'Angelo A, Salvadeo S, Ferrari I, Fogari E, et al., Effect of pioglitazone and acarbose on endothelial inflammation biomarkers during oral glucose tolerance test in diabetic patients treated with sulphonylureas and metformin, J. Clin. Pharm. Ther. 2010; 35:565-579. https://doi.org/10.1111/j.1365-2710.2009.01132.x PMid:20831680

7. Derosa G, Maffioli P. Mini-Special Issue paper Management of diabetic patients with hypoglycemic agents α-Glucosidase inhibitors and their use in clinical practice, Arch. Med. Sci. 2012; 5:899-906. https://doi.org/10.5114/aoms.2012.31621 PMid:23185202 PMCid:PMC3506243

8. Holt R, Lambert K. The use of oral hypoglycaemic agents in pregnancy, Diabet. Med. 2014; 31:282-291. https://doi.org/10.1111/dme.12376 PMid:24528229

9. Syahrul I. et al. Synthesis of novel flavone hydrazones: In-vitro evaluation of α-glucosidase inhibition, QSAR analysis and docking studies Eur. J. Med. Chem., 2015; 105:156-170. https://doi.org/10.1016/j.ejmech.2015.10.017 PMid:26491979

10. Muhammad T. et al. Synthesis of novel inhibitors of α-glucosidase based on the benzothiazole skeleton containing benzohydrazide moiety and their molecular docking studies, Eur. J. Med. Chem, 2015; 92:387-400. https://doi.org/10.1016/j.ejmech.2015.01.009 PMid:25585009

11. Farman A, et al. Hydrazinyl arylthiazole based pyridine scaffolds: Synthesis, structural characterization, in vitro α-glucosidase inhibitory activity, and in silico studies, Eur. J. Med. Chem., 2017; 138:255-272. https://doi.org/10.1016/j.ejmech.2017.06.041 PMid:28672278

12. Flynn GL. Substituent constants for correlation analysis in chemistry and biology. By Corwin Hansch and Albert Leo. Wiley, 605 Third Ave., New York, NY 10016. 1979.

13. Golbraikh A, Tropsha A., Beware of Q2, J Mol Graph Model, 2002; 20:269-76. https://doi.org/10.1016/S1093-3263(01)00123-1 PMid:11858635

14. Krzywinski M, Altman N. Classification and regression trees. Nat Methods. 2017; 14(8):757. doi: 10.1038/nmeth.4370. https://doi.org/10.1038/nmeth.4370

15. Costa VG, Pedreira CE. Recent advances in decision trees: an updated survey. Artif Intell Rev. 2023; 56:4765-4800. https://doi.org/10.1007/s10462-022-10275-5

16. Ahn S, Lee SE, Kim M. Random-forest model for drug-target interaction prediction via Kullback-Leibler divergence. J Chemin-2022; 14:67. https://doi.org/10.1186/s13321-022-00644-1 PMid:36192818 PMCid:PMC9531514

17. Kapsiani S, Howlin BJ. Random forest classification for predicting lifespan-extending chemical compounds. Sci Rep. 2021;11 https://doi.org/10.1038/s41598-021-93070-6 PMid:34226569 PMCid:PMC8257600

18. Yu F, Wei C, Deng P, Peng T, Hu X. Deep exploration of random forest model boosts the interpretability of machine learning studies of complicated immune responses and lung burden of nanoparticles. Sci Adv. 2021; 7 https://doi.org/10.1126/sciadv.abf4130 PMid:34039604 PMCid:PMC8153727

19. Tharwat A. Parameter investigation of support vector machine classifier with kernel functions. Knowl Inf Syst. 2019; 61:1269-1302. https://doi.org/10.1007/s10115-019-01335-4