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Original Article

2D/3D-QSAR, DOCKING AND OPTIMIZATION OF 5-SUBSTITUTED-1H-INDAZOLE AS INHIBITORS OF GSK-3β

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ABSTRACT

Objective: Glycogen synthase kinase-3 beta (GSK-3β) plays a crucial role in several human diseases. GSK-3β is being one of the most attractive therapeutic targets for several decades across the research communities to discover new potent and selective inhibitors of GSK-3β. The objective of the research is to develop new compounds based on the QSAR and molecular docking studies.

Methods: 2D/3D QSAR studies were conducted on a series of 5-substituted Indazole derivatives in order to optimize the GSK-3β inhibitors. Optimized inhibitors were subjected to molecular docking studies to find best inhibitors towards GSK-3β.

Results: The significant QSAR model-3 (2D) and model-6 (3D) elucidate that T_C_N_5, T_2_N_0, SlogP, electrostatic potential (E_451, E_229) and hydrophobicity (H_1052) are important descriptors to conclude the biological activities of compounds. Docking study illustrates Val135, Gln185, Arg141 and Asp200 were essential interacting residues in the active site of the receptor with ligands. Based on QSAR models, 450 compounds were optimized and validated through docking studies.

Conclusion: The best 31 optimized compounds, which showed good interaction energy, docking score and preferred interactions were selected as GSK-3β inhibitors.

Keywords: Glycogen synthase kinase-3 Beta, GSK-3β, QSAR, Docking, Indazole.

INTRODUCTION

Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine/threonine kinase and exists with two isoforms GSK-3α and GSK-3β in mammals with nearly 98% of identity but functionally not identical [4, 16], it is also known as human tau protein kinase (TPK I) [3]. Predominantly, various proteins are regulated through GSK-3β and involved in neuronal growth, metabolic homeostasis [10] and inflammation [15]. Because of the distinctive roles of GSK-3β in pathophysiological, it is considered as a potential therapeutic target for the treatment of diabetes [9], Alzheimer's disease [6], Mood disorders [7]. In addition to that GSK-3β is a pluripotent kinase [12] involved in cell functions and also reported its role in cancers such as Lung, Breast, colon, ovarian [5, 11, 9]. GSK-3β is also a potential therapeutic target for cancer [8]. As the inhibition of GSK-3β is a prospective approach to treat various diseases conditions, it gets more attention in drug discovery industry and academy.

The present study describes the structural features of 5-substituted Indazole derivatives as inhibitors of GSK-3β and the predictive models to find relevant features of molecules by Quantitative Structure–Activity Relationships (QSAR) and Molecular docking. QSAR is being applied across various domains to know the structural features of small molecules. Molecular docking studies are constantly used to realize the ligand and receptor interaction. The 5-substituted indazole are potent kinase inhibitors [1]. 2D/3D QSAR and docking studies are performed on 5-substitued-1H-indazole derivatives to get the insight about necessary structural features to optimize ligand to enhance biological activities. Based on significant 2D/3D QSAR models, the Indazole derivatives were optimized and the effectiveness of optimized compounds towards GSK-3β were validated by using molecular docking studies.

MATERIALS AND METHODS

Dataset

In this study, a series of 42 molecules belongs to GSK-3β inhibitors and their binding affinity (Ki in μM) were taken from the literature [1-2]. The compounds were sketched using ISIS draw. All molecules were optimized using Merck molecular force field MMFF as force field and charge. The inhibitors which had pKi as >5.00uM were considered as 5.00uM. The negative logarithm of the measured binding affinity [pKi = -log (Ki)] were considered as dependent variable for 2D/3D-QSAR analysis. The log pKi value ranges from 5.26 to 8.00. The 5-substitued-1H-indazole derivatives listed in Table1.

Selection of Training set and Test set

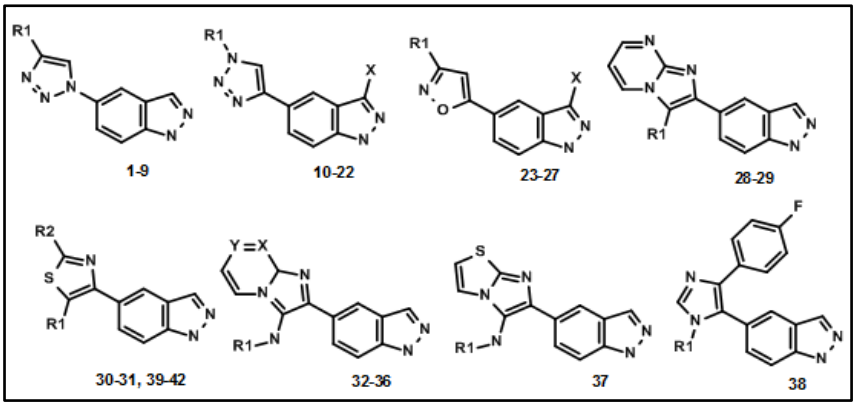
The dataset of 42 molecules were divided into training set (34 compounds) and test set (8 compounds) by sphere Exclusion Method. The various dissimilarity values were tried to get a desired division of training and test set. The accuracy of selection of test and training sets was confirmed by unicolumn statistics of test and training sets which is displayed in Table2. The maximum of the training set was more than that of the test set and the minimum of the training set was less than or equal to that of the test set.

QSAR Modeling

QSAR or quantitative structure–property relationships (QSPR) is a mathematical method to relate the set of compounds to its biological activity or property. QSAR study was applied using Vlife MDS software [14] to establish correlation between 2D/3D descriptors and experimental activity for set of compounds using statistical methods.

A total of 252 descriptors like element counts, molecular weight, topological index, molecular refractivity, log P, Baumann alignment independent topological etc., were considered to generate 2D-QSAR model. The hydrophilic, steric and electrostatic field's descriptors were calculated with default values of 30.0 and 10.0 kcal/mol as cutoff to generate significant 3D QSAR models. The activity field was considered as dependent variable and 2D/3D descriptors were considered as independent variables. The different QSAR models were generated by using multiple linear regression (MLR), principal component regression (PCR) and partial least squares (PLS) methods and variable selection methods like Forward–Backward stepwise, Genetic Algorithm and Simulated Annealing.

Table 1: Structure, experimental biological activities of 5-substitued-1H-indazole derivatives



CPD	R1	R2	X/Y	Ki (uM)
1	CH3CH2CH2-	-	-	2.026
2	CH3OCH2-	-	-	5.450
3	OH-CH2(CH2)2-	-	-	5.216
4	C3H5-	-	-	3.466
5	C5H9-	-	-	1.298
6	C6H11-CH2-	-	-	0.891
7*	C6H5-CH2-	-	-	0.542
8	C6H5-(CH2)2-	-	-	0.446
9*	C6H5-(CH2)3-	-	-	0.528
10	H	-	-	0.448
11*	C6H5-CH2-	-	-	0.039
12	C6H5-CH2-	-	X=NH2	0.265
13*	2-Cl-C6H5-CH2-	-	-	0.045
14	3-Cl-C6H5-CH2-	-	-	0.023
15*	4-Cl-C6H5-CH2-	-	-	0.197
16	2-F-C6H5-CH2-	-	-	0.091
17	3-F-C6H5-CH2-	-	-	0.026
18	4-F-C6H5-CH2-	-	-	0.070
19	3-CH3-C6H5-CH2-	-	-	0.070
20*	2-Cl,3-Cl-C6H5-CH2-	-	-	0.048
21	3-Cl, 6-Cl-C6H5-CH2-	-	-	0.016
22	3-Cl, 5-Cl-C6H5-CH2-	-	-	0.028
23	C6H5-CH2-	-	X=H	0.572
24	C6H5-CH2-	-	X=NH2	0.450
25	CH3-(CH2)2-	-	X=H	2.530
26	CH3-NHC(O)-	-	X=H	4.272
27	PIPERIDINE-1-YL-CH2-	-	X=H	3.810
28	H	-	-	0.141
29	C6H5-	-	-	0.010
30	H	CH3	-	2.861
31	H	NH2	-	4.472
32	C6H11-	-	X=C; Y=C	2.611
33	C6H11-	-	Y=C; X=N	0.010
34*	(CH3)2-CH-	-	Y=C; X=N	0.017
35	CH3-(CH2)3-	-	Y=C; X=N	0.019
36	4-Cl-C6H5-	-	Y=C; X=N	0.121
37	C6H11-	-	-	0.642
38	(CH3)2N-(CH2)2-	-	-	5.450
39	H	CH3CH2NH-	-	3.925
40	H	C6H5-NH-	-	0.289
41	C6H6-	C6H5-NH-	-	5.450
42*	C6H6-	C6H5-CH2-NH-	-	3.402

*Test set

Table 2: Unicolumn statistics of training and test sets

Set	Average	Max	Min	Std dev.	Sum
2D QSAR					
Training	6.3659	8.0000	5.2640	0.9251	216.4410
Test	6.8202	7.7700	5.4680	0.7763	54.5620
3D QSAR					
Training	6.4551	8.0000	5.2640	0.8816	200.1090
Test	6.4449	8.0000	5.2640	1.0238	70.8940

Regression analysis

For 2D-QSAR, all 42 molecules of 5-substituted-1H-indazole derivatives were subjected to regression analysis using MLR, PCR, and PLS as model building methods. 3D-QSAR models were generated using k-nearest neighbour (kNN) principle with stepwise, genetic algorithm and simulated annealing methods.

The statistical parameters, n (number of compounds in regression), r^2(coefficient of determination),k (number of descriptors in a model), F (F-test), pred_r^2 (cross-validated correlation coefficients), pred_r^2se (coefficient of correlation of predicted data set), r2_se and q^2_se were used to evaluate generated QSAR models. The developed QSAR models were validated by using external validation method.

Alignment

Molecular alignment is a key step to develop various reliable 3D-QSAR models. 42 molecules were aligned by template based technique. The common structure 1H-Indazole was used as template. The aligned structures were used for 3D-QSAR study. A common rectangular grid was generated around the aligned molecules. The alignment of all molecules is shown in the Figure 1.

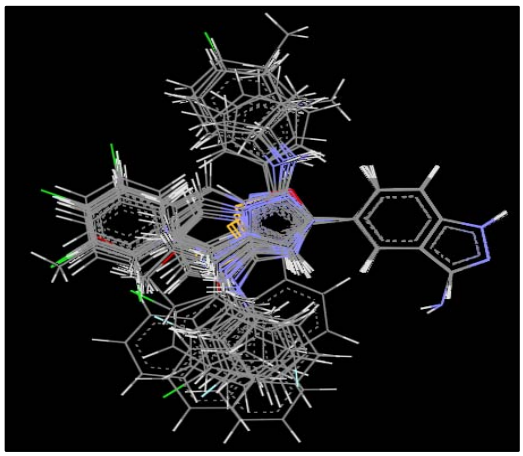


Fig. 1: Molecules alignment of 5-substituted-1H-indazole derivatives

Molecular docking

Molecular docking was carried out to get better insight about interaction between protein and molecules. It is used to find energetically favourable conformation of ligand in the active site of protein. The protein coordinates of human GSK-3β (PDB ID: 1Q4L) was retrieved from Protein data bank (http: //www. pdb. org) and used as protein structure. Protein preparation steps includes removal of chain B and water molecules, cavity prediction, assigning bonds, bond order and hybridization, adding explicit hydrogen's, assigning charges were done for chain A of 1Q4L by using Molgro Virtual Docker (MVD) trial version. MVD was used for docking as it is showed higher docking accuracy [13].

The binding cavities for chain A were found using cavity detection algorithm and the binding region was defined as X (39.83), Y (6.26), and Z (34.23) with a resolution of 0.30 Å and radius of 15 Å. The binding cavity volume (128.512 Å) was considered for docking studies. The reference ligand (679 from 1Q4L) was docked with MolDock Score [GRID], Mol Dock SE algorithm, number of runs was 10 and max iterations was 1500, to validate the docking settings. The measured RMSD between docking simulation (yellow) and the original ligand (green) is 1.45Å with -150.491dockscore, -138.12 interaction energy. Generally the docking method is considered as successful if the RMSD value is less than 2Å. The both ligand 679 and docking simulation ligand 679 interacted to the same residues Asp133, Val135, Arg141 and Gln185of 1Q4L Figure 2. The validated docking setting was used to perform docking calculation of Indazole derivatives. After docking, each pose of the ligands was manually analyzed to find best conformation based on interaction energy, interacting residues of ligand with the protein.

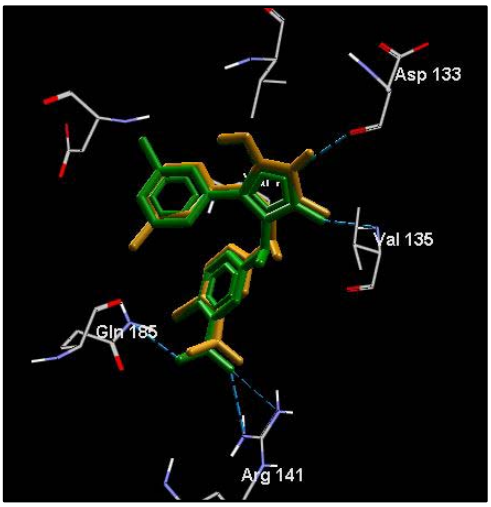


Fig. 2: The ligand 679 (green) and docking simulation ligand679 (yellow)

RESULTS AND DISCUSSION

The 2D-QSAR significant models were generated using Multi linear regression, partial least square and principal component regression by forward-backward variable selection method.

Model-1 (MLR)

n = 34; Degree_of_freedom = 28; r^2 = 0.8345; q^2 = 0.7544; F_test = 28.2363; r^2_se = 0.4086; q^2_se = 0.4977; pred_r^2= 0.6887; pred_r^2se = 0.5109

pKi50 = + 0.0142(T_2_F_7) - 0.3144(Nitrogens Count) + 0.2672(chi4) - 0.6610(T_N_N_5) + 1.8058(T_2_N_0) + 1.5853

The Model 1 has correlation coefficient (r^2) of 0.8345, significant cross validated correlation coefficient (q^2) of 0.7544, F test of 28.2363 and degree of freedom 28. The model is validated by best_ran_r^2 = 0.42629, best_ran_q^2 = 0.17788, Z score_ran_r^2 = 7.14878 and Z score_ran_q^2 = 5.70501.

Model-2 (PLS)

n = 34; Degree_of_freedom = 29; r^2= 0.8818; q2 =0.7550; F_test= 54.0711; r^2_se = 0.3393; q^2_se = 0.4884; pred_r^2 = -0.0164; pred_r^2se = 0.9232

pKi50 = + 0.1772 (T_C_N_5) - 0.4006 (H-Acceptor Count) - 0.0000 (Ipc Average) + 0.0964 (T_2_2_3) + 0.4953 (T_N_N_4) + 3.4710.

The Model 2 has correlation coefficient (r^2) of 0.8818, significant cross validated correlation coefficient (q^2) of 0.7550, F test of 54.0711 and degree of freedom 29. The model is validated by best_ran_r^2 = 0.41535, best_ran_q^2 = 0.09836, Z score_ran_r^2 = 8.61461 and Z score_ran_q^2 = 4.76428.

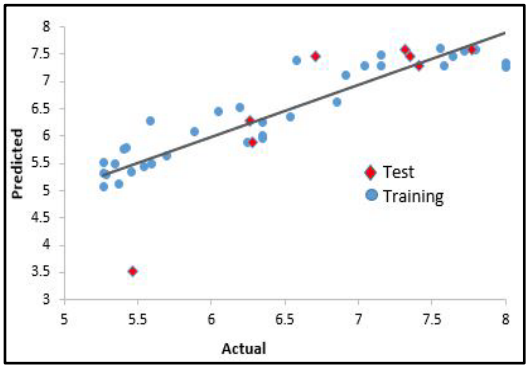
Model-3 (PCR)

n = 34; Degree_of_freedom = 29; r^2 = 0.8672; q^2 = 0.8212; F_test = 47.3469; r^2_se = 0.3596; q^2_se 0.4173; pred_r^2 =0.7102; pred_r2se = 0.4072

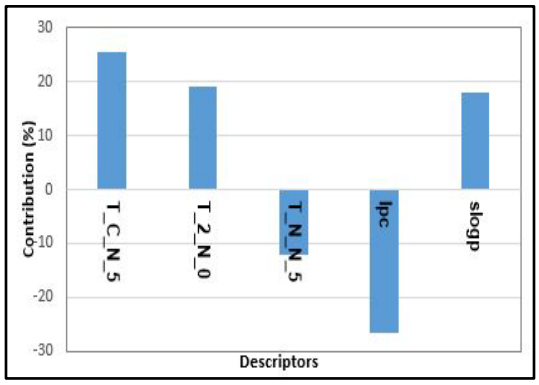
pKi50 = + 0.1347 (T_C_N_5) + 0.7747 (T_2_N_0) - 0.2878 (T_N_N_5) - 0.0000 (Ipc) + 0.3184 (slogp) + 2.4170

The Model 3 has correlation coefficient (r^2) of 0.8672, significant cross validated correlation coefficient (q^2) of 0.8212, F test of 47.34 and degree of freedom 29. The model was validated by best_ran_r^2 = 0.36941, best_ran_q^2 = 0.13846, Z score_ran_r^2 = 9.25745 and Z score_ran_q2 = 7.36423. The statistically significant model-3 reveals that T_C_N_5 (25.50%) the number of carbon atoms (single, double or triple bonded) separated from nitrogen atom by 5 bond distance in a molecule (C-C-C-C-C-N), T_2_N_0

(19.17%) is count of number of double bonded atoms (i. e., any double bonded atom, T_2) separated from nitrogen atoms by a zero bond distance and slogp (18.03%) descriptor signifies the Octanol/water partition coefficient. These descriptors are directly proportional to activity of molecules. T_N_N_5 and Ipc are negatively contribute towards biological activity. The plot of Actual vs. Predicted activity is shown in Figure 3. and predicted pKi of compounds are shown in Table3.



(a)



(b)

Fig. 3: (a) Graph of experimental versus predicted pKi (b) Contribution chart of descriptor for model 3

The 3D-QSAR significant models were generated using k-nearest neighbour (kNN) principle with stepwise, genetic algorithm and simulated annealing methods.

Model 4

k Nearest Neighbour = 2; n = 34, Degree_of_freedom = 31; q2 = 0.6051; q2_se = 0.5813; pred_r2 = 0.4966; pred_r2se = 0.6498; Selected Descriptors and range = E_484 (-1.4520, -1.2580) and H_312 (0.4730, 0.5620)

pKi50 = E_484 (-1.4520, -1.2580) H_312 (0.4730, 0.5620)

Model 4 describes that negative electrostatic potential (E_484) and hydrophobicity (H_312) determine the biological activity of compounds.

Model 5

k Nearest Neighbour = 5; n = 34, Degree_of_freedom = 30; q^2 = 0.4877; q^2_se =0.6621; pred_r^2 = 0.3794; pred_r^2se = 0.7214; Selected Descriptors and range = E_1030 (-1.8550, -1.5980), E_984 (1.5100, 2.2200) and H_641 (0.1780, 0.3020)

pKi50 = E_1030 (-1.8550, -1.5980) E_984 (1.5100, 2.2200) H_641 (0.1780, 0.3020)

In this model three descriptors hydrophobicity, positive and negative electrostatic potential has major contribution in inhibitory activity.

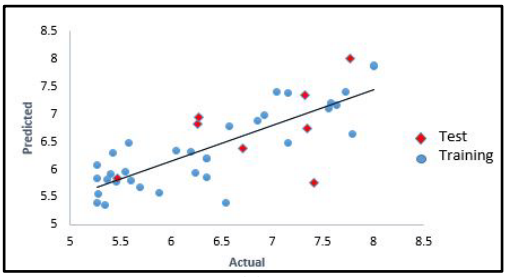
Model 6

k Nearest Neighbour = 2; n = 34, Degree_of_freedom = 28; q^2 =0.7153; q2_se =0.4936; pred_r^2 =0.2938; pred_r^2se = 0.7696; Selected Descriptors and range = E_451 (1.9000, 1.9600), E_229 (2.9320, 3.4120), S_914 (-0.0020 -0.0020), S_1080 (-0.0070, -0.0060) and H_1052 (0.3500, 0.3830)

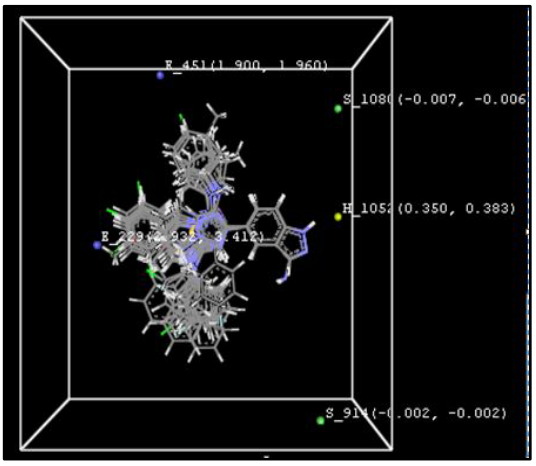
pKi50 = E_451 (1.9000, 1.9600) E_229 (2.9320, 3.4120) S_914 (-0.0020 -0.0020) S_1080 (-0.0070, -0.0060) H_1052 (0.3500, 0.3830)

Model 6 found to be statistically significant with respect to external and internal predictive ability. The model showed internal predictive ability of about 70% (q^2=0.7153) and external predictive ability of about 30 %(pred_r^2=0.2938). This model explains the contributions of electrostatic (E_451, E_229) and hydrophobicity (H_1052) descriptors in the activity of 5-substituted Indazole based GSK-3β inhibitors.

The plot of Actual vs. Predicted activity is shown in Figure 4. And the predicted pKi values are shown in Table3.



(a)



(b)

Fig. 4: (a) Graph of experimental versus predicted pKi (b) Important steric, electrostatic point contribution for model 6 with values.

In the present study, Model 3 from 2D QSAR and Model 6 from 3D-QSAR were selected as best models based on r^2, q^2. The 2D QSAR model explainsthatT_C_N_5, T_2_N_0 and slogp descriptors enhance the activity of compounds. In 3D QSAR, model 6 explains E_451, E_229 (electrostatic) and H_1052, (hydrophobicity) play vital roles in enhancing the activity of the compounds. These models were useful in optimizing the activity of 5-substituted Indazole analogs towards GSK-3β.

Docking

The 14 molecules of 5-substituted-1H-indazole derivatives were selected for docking studies based on Ki values ranges from 0.01uM to 0.091uM and docking studies results were shown in the Table 4 with MolDcok score, interacting residues, H-bond length for each molecule. In each docking run, the best poses were selected based on Moldock score and binding energy.

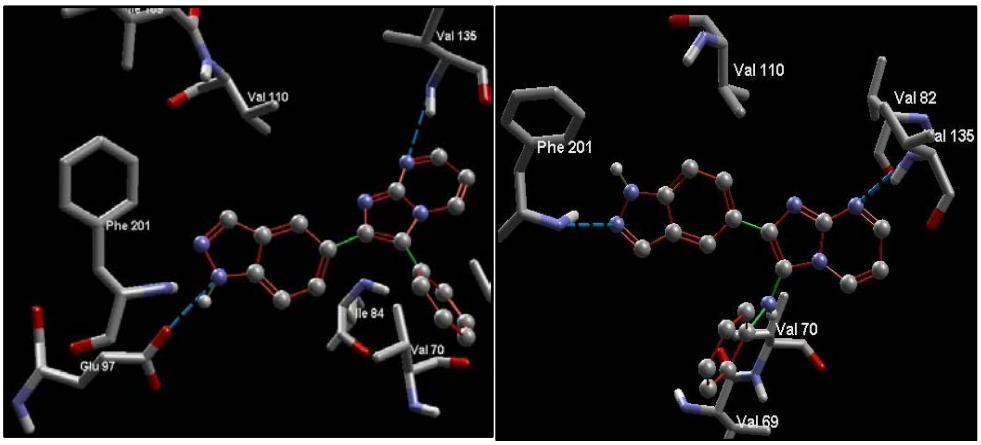
Table 3: Predicted values for statistically significant models

S. No.	Activity (PKi)	Model-3Predicted	Residue	Model-6Predicted	Residue
1	5.693	5.63	0.06	5.68	0.01
2	5.264	5.33	-0.06	5.40	-0.14
3	5.283	5.30	-0.01	5.55	-0.27
4	5.460	5.33	0.13	5.79	-0.33
5	5.887	6.10	-0.21	5.58	0.30
6	6.050	6.45	-0.40	6.35	-0.30
7	6.266	6.28	-0.01	6.81	-0.54
8	6.351	6.00	0.35	5.86	0.49
9	6.277	5.88	0.39	6.94	-0.66
10	6.349	6.25	0.10	6.20	0.15
11	7.409	7.30	0.11	5.75	1.66
12	6.577	7.39	-0.81	6.77	-0.19
13	7.347	7.46	-0.11	6.75	0.60
14	7.638	7.46	0.17	7.15	0.49
15	6.706	7.46	-0.75	6.37	0.33
16	7.041	7.29	-0.25	7.39	-0.35
17	7.585	7.30	0.28	7.21	0.38
18	7.155	7.30	-0.14	7.39	-0.24
19	7.155	7.49	-0.33	6.47	0.68
20	7.319	7.59	-0.27	7.35	-0.03
21	7.796	7.59	0.20	6.64	1.16
22	7.553	7.61	-0.06	7.11	0.44
23	6.243	5.88	0.36	5.95	0.29
24	6.347	5.97	0.38	6.20	0.15
25	5.597	5.41	0.18	5.79	-0.19
26	5.369	5.07	0.30	5.81	-0.44
27	5.419	5.79	-0.37	6.29	-0.87
28	6.851	6.97	-0.11	6.89	-0.04
29	8.000	8.15	-0.15	7.89	0.11
30	5.543	5.52	0.02	5.97	-0.42
31	5.349	5.47	-0.12	5.36	-0.01
32	5.583	6.27	-0.69	6.49	-0.90
33	8.000	7.35	0.65	7.87	0.13
34	7.770	7.58	0.19	8.00	-0.23
35	7.721	7.57	0.15	7.41	0.31
36	6.917	7.12	-0.20	6.99	-0.07
37	6.192	6.52	-0.32	6.31	-0.12
38	5.264	5.51	-0.25	5.84	-0.57
39	5.406	5.46	-0.05	5.92	-0.51
40	6.539	6.24	0.30	5.40	1.14
41	5.264	4.98	0.28	6.09	-0.83
42	5.468	3.29	2.18	5.83	-0.37

The Table 4 indicates the reasonable Moldock score ranges from -137.063 to -116.562 for stable interaction between ligand and protein. The highly active compounds of 29 and 33 resulted with highest docking score of -130.097 and -125.554,respectively. The results explain that the Indazole derivatives interact with Val135, Gln185, Asp200, and Arg141 residues in the active site through the nitrogen atom of cyclic ring substituted in the 5th position of Indazole derivatives is one of the crucial factors for more binding affinities. Figure 5a shows the binding image of compound 29 shows interaction energy -137.83 kcal/mol and -130.097 MolDock score forming favourable interaction with Val135 and Glu97 amino acids and Figure 5b shows binding image of compound 33 shows interaction energy -127.57 kcal/mol and -125.554 MolDock score forming favourable interactions with Val135 and Phe201 amino acids.

Table 4: Docking result of experiment compounds

Cpd. No	Ki (uM)	MolDock Score	Interaction Energy	Residue	H-bond length
11	0.039	-116.562	-128.59	Glu97, Cys199	3.11,3.25
13	0.045	-118.013	-122.11	Val135, Asp200,Glu97	3.30,3.13,3.42
14	0.023	-120.844	-133.79	Val135, Arg141, IIe62	(3.23,3.10),3.23, 3.14
16	0.091	-117.417	-124.03	Val135	3.32
17	0.026	-117.573	-120.00	Gln185, Tyr134,Val135	(3.04,3.16),3.05, 3.08
18	0.07	-118.108	-118.70	Gln185, Tyr134, Pro136	3.16,2.97,2.84
19	0.07	-125.66	-114.34	Gln185,Glu97, Cys199	(3.18,3.15),3.09,3.00
20	0.048	-126.385	-130.92	Phe201, Glu97	3.48,3.01
21	0.016	-125.964	-131.29	Gln185, Glu97	3.32,3.24
22	0.028	-130.113	-115.25	Val135,Glu97,Phe201, Asp200	3.39,3.07,3.39, 3.20
29	0.01	-130.097	-137.83	Val135, Glu97	3.28, 2.90
33	0.01	-125.554	-127.57	Val135, Phe 201	2.84, 3.15
34	0.017	-131.935	-98.58	Val135, Glu97	3.09, 2.82
35	0.019	-137.063	-106.53	Val135, Asp200	2.90, 3.36

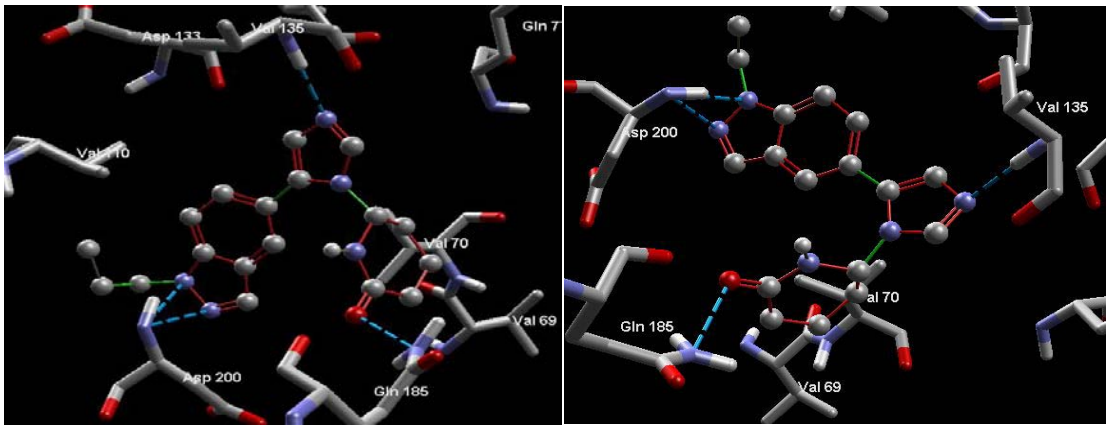


(a) **(b)**

Fig. 5: Hydrogen bond interaction between (a) compound 29 and (b) compound 33 with receptor

Based on QSAR Models (3&6) 450 new compounds were designed by substituting various substituents (methyl; ethyl; n-propyl; hydrogen; amino; hydroxy; acetyl amino; 1H-imidazol-4-yl; cyclohexylamino; pyrimidine-4-yl; 6-oxo-2-piperidyl and 3-OH-pyridin-4-yl) in skeleton structures which are shown in Table1. The docking of GSK-3β (1Q4L) receptor with all newly designed ligands exhibited well established bonds with amino acids in the receptor's active pocket. Most of the compounds showed better interaction energy and MolDock Score than experimental compounds. Figure 6a shows docking images of compound Id 416 shows interaction energy of -139.58 kcal/mol and MolDock score of -148.49 having interaction with Val135, Gln185 and Asp200 and Figure 6b shows docking images of compound Id 397 shows interaction energy of -120.99 kcal/mol and -145.29 having interactions with Val135,Gln185 and Asp200

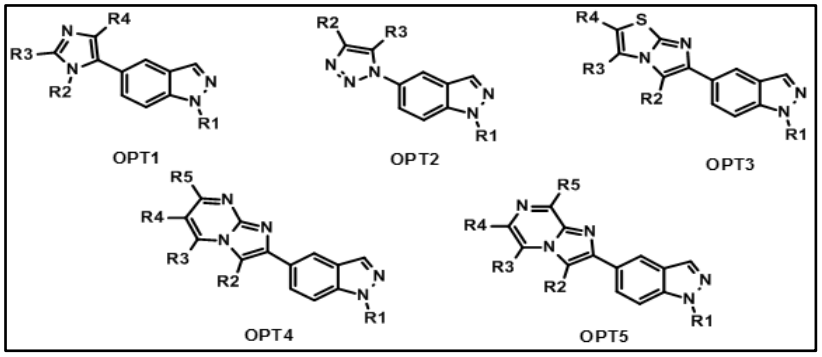
Based on the docking score and interaction energy, best 31 compounds were selected and listed in Table 5 and their docking score, interaction energy, interacting residues and H-bond distance were reported in Table 6. Docking studies reveal that 31 optimized ligands showed good binding with favourable hydrogen bond interaction toward GSK-3β. Optimized scaffold OPT5 derivatives (Cpd_ID141, 139, 160, 210, 161 and 152) show good interaction with GSK-3β.



(a) **(b)**

Fig. 6: Hydrogen bond interaction compounds (a) Cpd_ID 416 and (b)Cpd_ID397with receptor

Table 5: Newly designed compounds



Cpd_ID	Core	R1	R2	R3	R4	R5
416	OPT1	n-propyl	6-oxo-2-piperidyl	H	H	-
397	OPT1	ethyl	6-oxo-2-piperidyl	H	H	-
308	OPT3	n-propyl	pyrimidine-4-yl	H	H	-
46	OPT4	n-propyl	H	3-OH-pyridin-4-yl	H	H
107	OPT4	H	3-OH-pyridin-4-yl	H	H	H
468	OPT2	n-propyl	H	6-oxo-2-piperidyl	-	-
282	OPT3	H	1H-imidazol-4-yl	H	H	-
453	OPT1	n-propyl	H	3-OH-pyridin-4-yl	H	-
141	OPT5	H	Pyrimidine-4-yl	H	H	H
435	OPT1	ethyl	H	6-oxo-2-piperidyl	H	-
134	OPT4	ethyl	6-oxo-2-piperidyl	H	H	H
434	OPT1	ethyl	H	3-OH-pyridin-4-yl	H	-
126	OPT4	methyl	3-OH-pyridin-4-yl	H	H	H
118	OPT4	n-propyl	1H-imidazol-4-yl	H	H	H
71	OPT4	H	H	H	6-oxo-2-piperidyl	H
68	OPT4	H	H	H	acetylamino	H
139	OPT5	H	acetylamino	H	H	H
514	OPT2	ethyl	3-OH-pyridin-4-yl	H	-	-
78	OPT4	n-propyl	H	H	cyclohexylamino	
471	OPT2	n-propyl	H	cyclohexylamino	-	-
36	OPT4	H	H	6-oxo-2-piperidyl	H	H
160	OPT5	methyl	6-oxo-2-piperidyl	H	H	H
210	OPT5	H	H	H	acetylamino	H
161	OPT5	methyl	3-OH-pyridin-4-yl	H	H	H
152	OPT5	n-propyl	3-OH-pyridin-4-yl	H	H	H
108	OPT4	H	1H-imidazol-4-yl	H	H	H
456	OPT1	n-propyl	H	pyrimidine-4-yl	H	-
100	OPT4	ethyl	H	H	1H-imidazol-4-yl	H
347	OPT3	n-propyl	H	6-oxo-2-piperidyl	H	-
55	OPT4	methyl	H	3-OH-pyridin-4-yl	H	H
10	OPT2	ethyl	6-oxo-2-piperidyl	H	-	-

Table 6: Docking results of newly designed compounds

Cpd_ID	MolDock Score	Interaction Energy	Residue	Hbond length
416	-148.49	-139.58	Val135,Gln185,Asp200	3.31,2.91,3.16
397	-145.29	-120.99	Val135,Gln185,Asp200	3.13,2.84,3.17
308	-148.36	-126.58	Asp200,Val135	3.00, 3.22
46	-142.55	-145.89	Val135,Gln185,Asp200,Tyr134, Lys85	2.99,2.94,3.41,3.09,3.22
107	-140.87	-141.58	Val135,Gln185,Asp200, Phe201,Glu97	3.15,2.79,3.23,3.21,2.70
468	-140.67	-134.78	Val135,Gln185,Asp200	3.10,2.61,3.22
282	-139.96	-124.90	Asp133,Gln185	2.93,2.62,(3.20,3.43)
453	-139.40	-143.90	Arg141,Val135,Asp200	2.77,(3.13,2.63),(3.22,3.19)
141	-138.78	-141.48	Val135,Gln185,Cys199,Glu97, Phe201	3.10,2.90,2.81,2.56,3.39
435	-137.07	-137.88	Val135,Tyr134,Asp200	(3.30,2.94),2.76,(3.15,3.16)
134	-136.38	-139.93	Val135,Gln185,Asp200	3.16,3.09, (3.28,3.23)
434	-136.01	-138.50	Val135,Arg141,Asp200	(3.15,2.63),2.81,(3.15, 3.16)
126	-135.65	-134.85	Val135,Gln185,Asp200, Phe201	3.29,2.92,3.21,3.39
118	-135.32	-127.54	Val135,Gln185,Asp200,Lys85	2.62,3.07,3.14,2.94
71	-134.52	-142.18	Val135,Arg141,Asp200,Phe201, Glu97	3.28,3.24,3.20,3.29,2.73
68	-134.34	-135.16	Val135,Arg141,Asp200,Phe201, Glu97	3.20,3.24,3.24,3.34,2.73
139	-134.17	-130.92	Val135,Gln185,Glu97	3.09,2.92,2.58
514	-134.00	-136.02	Val135,Arg141,Asp200	(2.63,3.20),3.25,(3.17,319)
78	-133.62	-136.57	Val135,Arg141	3.29,(2.98,3.30)
471	-133.46	-125.39	Val135,Gln185	3.22,(2.90,3.06)
36	-133.12	-138.32	Val135,Arg141,Glu97	3.38,2.91, 2.93
160	-133.04	-134.64	Val135,Gln185,Asp200	2.90,3.17, (3.13, 3.32)
210	-132.22	-133.96	Val135,Arg141,Glu97	3.24,3.26, 2.71
161	-132.10	-129.92	Val135,Gln185,Asp200,Cys199	3.23,3.10, 3.38, 2.59
152	-132.09	-136.18	Val135,Asp133,Gln185, Asp200	3.02,2.80,3.29, 3.19
456	-131.77	-141.36	Val135, Arg141, Asp200	3.12,2.98, 3.11
100	-131.72	-131.07	Val135, Asp200, Lys85	3.07,3.07, 3.42
347	-131.68	-127.52	Val135, Arg141	3.39,(3.05,3.08)
55	-131.63	-135.45	Val135, Arg141, Asp200	3.21,3.31,(3.15,3.27)
10	-131.21	-134.35	Val135, Asp200, Tyr134	3.16, (3.13, 3.096), 3.18
108	-131.84	-126.01	Asn 64,Asp133,Asp200,Phe 201	3.07,2.59,(3.14,3.06,3.11), 3.55

CONCLUSION

In present study 2D/3D QSAR and docking studies on series of Indazole derivatives were applied successfully to identify the necessary structural, substituent requirements and potential interaction of 5-subsituted Indazole derivatives of GSK-3β inhibitors. 2D-QSAR descriptors T_C_N_5, T_2_N_0, slogp descriptors and 3D-QSAR descriptors E_451, E_229 (electrostatic) and H_1052, (hydrophobicity) enhance the binding affinities of compounds. Docking study showed the important interacting residues in the active site of receptor are Val135, Gln185, Arg141 and Asp 200 with ligands. Optimized 31 ligands have good docking score and favourable interactions in the active site. These compounds seem to be having more binding affinities towards GSK-3β. As per our knowledge these compounds have not been reported as potential inhibitors so far. Therefore, the optimized molecules could be new potential candidates as GSK-3β inhibitors.

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Authors' Statement

The authors declare no conflict of interest.

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