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3D-QSAR AND MOLECULAR DOCKING STUDIES ON BISARYLMALEIMIDE SERIES AS GLYCOGEN SYNTHASE KINASE3B INHIBITORS

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ABSTRACT

The three dimensional quantitative structure activity relationship (3D-QSAR) models were developed for 30 bisarylmaleimide compounds inhibiting the glycogen synthase kinase-β (GSK3β). The studies included atom based 3D-QSAR model was developed for selected 30 compounds. The model showed a satisfactory statistical significance: (r^2 0.9691, r^2cv 0.7876) were found to be more informative in pinpointing the structural basis for the observed quantitative differences of kinase inhibition. The results of the best QSAR model were further compared with structure based investigations using docking studies with x-ray crystal structure of gsk3 domine (pdb. Id. 1R0E).

Key words: GSK-3β inhibitors, Kinase inhibitors, Bis aryl maleimides, Docking studies and QSAR studies.

INTRODUCTION

The glycogen synthase kinase3β was originally identified and studied for its functions in the regulation of glycogen synthase as rate limiting enzyme in glycogen biosynthesis[1].it is serine /threonine kinase comprising two isoforms (α and β) in mammals. These isoforms share high homology (>90%) at the catalytic domine and expressed ubiquitously in cellular system and have similar biochemical properties[2].GSK3β has multiple substrates and plays a critical role in glucose homeostasis, CNS function[3], circadian rhythm, controlling cell cycle, neuro degeneration, chronic inflammatory diseases and cancer[4-5]. Fig1 shows some promising

classes of gsk3β inhibitors. However almost all of them were found to show affinity towards other kinase too. Maleimides of inhibitors (bisaryl maleimides)[4], anilino maleimides[5], bisindolyl maleimides[6], azaindolyl maleimides[7-10] have been reported to show a degree of selectivity toward gsk3β. All through a number of diverse classes of gsk3β inhibitor have been reported so far, the selectivity problem appears to hamper all efforts. This at least in part, stems from the fact that the kinase has the same natural substrates, ATP and most of the ligands act through competition with ATP. This calls for methodologies that tackle the non selectivity to address the design potential drug candidates of gsk3β inhibitors.

EXPERIMENTAL SECTIONS

Data set for analysis

A set of 30 compounds selected for gsk3β inhibitors was complailed (Table .1) the in vitro biological activity data reported as IC50 for inhibition of gsk3β by the bis aryl maleimide series[4] were used for the current study. The reference paper 46 compound were reported with their corresponding inhibitory activity expressed in IC50 values. Those molecules which do not have biological activity for inhibitor of the enzyme under study in exact numerical form were excluded from the analysis. Fallowing these 30 molecules was chosen for the current study. This was partitioned in to a training set (21) and test set (9) at random with bias given to structural diversity in both the training set and test set so as to form the standard 4:1 training set to test set ratio for a QSAR study. As biological data are generally skewed the reported IC50 values were converted in to pIC50.

Molecular modeling

The molecular modeling studies were performed using a Glide version 2012(Schrodinger 9.3). The bioactive conformation of a complex with GSK3β (pdb id. 1R0E) was used as a template for building the 3D structures of all the 30 compounds considered in this work. The electron withdrawing group was substituted on 8^{th} position of azaindole ring of bis aryl maleimides and used in this work. The structures of all molecules were constructed with the chemskech (ACD Lab) and chem. draw ultra 8.0. The energy minimizations were performed by ligprep using OPLS-2005 force field. The binding affinity of the inhibitors to the protein was than evaluated by the total glide docking energies. The 3D-QSAR models were developed using atom based QSAR by using PLS factor 4(partial least square).

Molecular alignments

One of the fundamental assumptions in 3D-QSAR studies is that a geometrical parallelism should exist between the modeled structures and that of the bioactive conformation. The spatial alignment of compounds under study is thus one of most sensitive and determining factors in obtaining a robust and meaning full model. In the present study the geometry optimized structures were aligned on the respective templates (GSK3β) by the flexible align data base command in glide (Schrodinger 9.3) using the maximum sub structure that is common to all and the molecular alignment image of selected 30 compounds are shown in fig 2.

Partial least square (PLS)

To quantify the relationship between the structural parameter and the biological activity the PLS algothism was used. The cross validation analysis was performed using leave one out (LOD) method where in one compound is removed from the dataset and its activity is predicted using the model derived from the rest of the dataset. The cross validation r^2 that resulted in optimum number of components and lowest standard error of prediction was taken. To speed up the analysis and reduce noise, a minimum column filtering values (σ) of 1.00 kcal/ mole was used for the cross validation. Final analysis (non cross validation) was performed to calculate conventional r^2 using the optimum number of component obtained from the leave one out cross validation analysis.

Predictive correlation coefficient (r^2 pred)

To further validate the derived model, biological activity of 9 test set molecules were predicted using model derived from the training set. Predictive r^2 value was calculated using formula

r^2pred= (SD-PRESS)/ SD

Where SD is the sum of squared deviation between the biological activities of the test set molecules and the mean activity of the training set molecules and PRESS is the sum of squared deviation between the actual and predicted activities of the test set molecules.

Molecular docking

X-ray crystal structure of GSK3β (pdb i.d. 1R0E) retrieved from protein data bank, docking of the designed molecules in to the binding pocket of gsk3β was carried out using the glide program available within Schrödinger 9.3 package. Glide employs a fast algorithm for flexible docking of small ligands in to fixed protein binding site using an incremental

construction process. To further evaluated the docking analysis the xpglide-score values were estimated using the glide modules of Schrodinger 9.3.

RESULTS AND DISCUSSION

The statistical details of the 3D-QSAR model are given in table 2. The actual and predicted activities obtained from atom based 3D-QSAR models of both the training set and test set are listed in table 3 &4 respectively. The scatter plots of actual versus predicted activities for both training set and test set molecules are shown in fig3 &4. The compounds 2, 6, 8, 10, 11, 12, 17, 21, 22, 27, 28 and 29 are better active than 1, 3, 4, 5, 14, 15, 16, 24 and 26 this steams from the fact that the more active compounds contain a bulky substituent that favors to enhancing gsk3β activity and electron withdrawing group (Bromine) is prefer at 8^{th} position on azaindole ring of bis aryl maleimides shown to exhibit enhancing the biological activity of molecules. The substitution at N^1 position on azaindole ring of bis aryl maleimides with acetyl and secondary amine group is optimum for inhibitory activity. The substitution with morpholine group on this position forward to enhancing the GSk3β inhibitory activity.

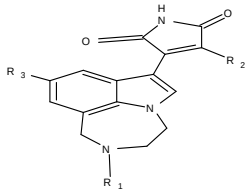
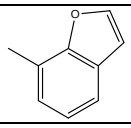
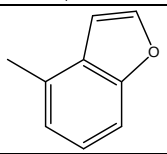
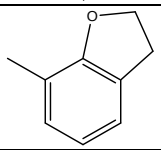
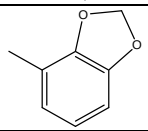
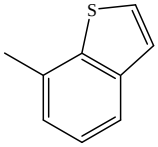
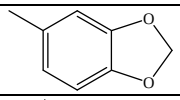
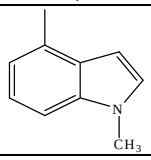
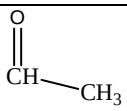
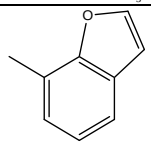
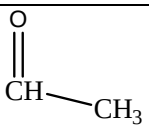
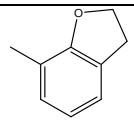
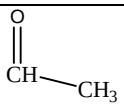
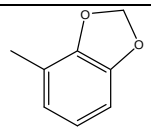
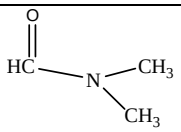
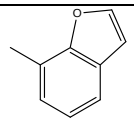
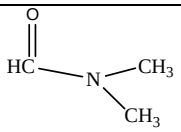
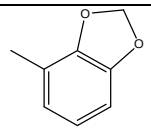
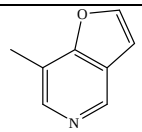
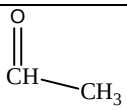
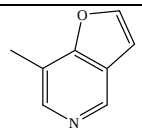
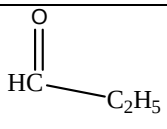
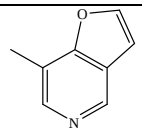
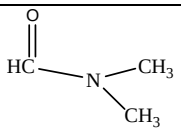
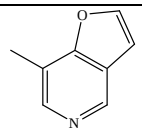
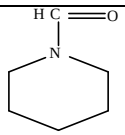
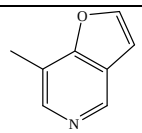
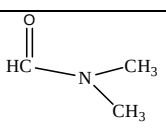
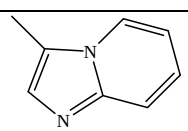
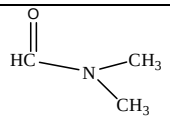
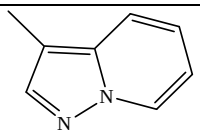
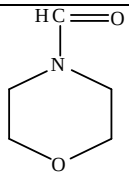
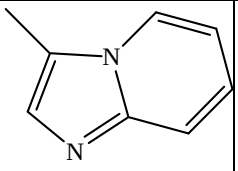
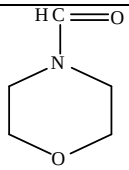
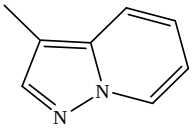
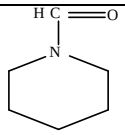
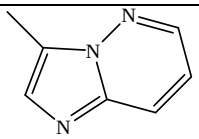
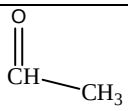
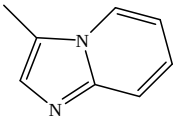
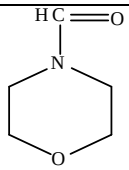
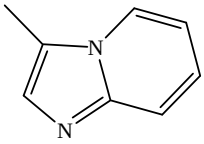
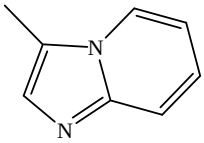
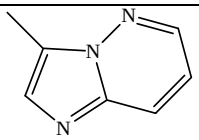
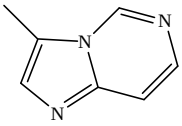
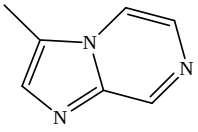
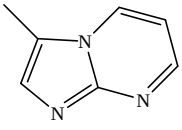


Table no. 1 showing the Structures of 30 GSk3β inhibitors in this study

S.No.	R_1	R_2	R_3	Actual activity (pIC50)
1	H		Br	8.469
2	H		Br	7.387
3	H		Br	8.481
4	H		Br	7.886
5	H		Br	7.347

6	H		Br	7.569
7	H		Br	7.481
8			Br	8.824
9			Br	8.959
10			Br	7.751
11			Br	8.569
12			Cl	8.495
13	H		Cl	8.495
14			Cl	9.046
15			Cl	9.000
16			Cl	8.921
17			Br	8.678
18			Br	8.796

19			Br	8.328
20			Br	8.886
21			Br	8.886
22			Br	9.135
23			Br	8.720
24			Br	9.097
25	H		Br	7.921
26	H		Br	8.319
27	H		F	6.481
28	H		F	7.222
29	H		F	6.921

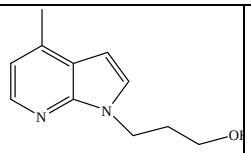
30	H		F	7.570

Table no. 2 showing the Statistical parameters

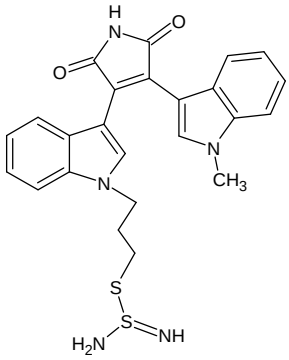
SD	R^2	R^2 CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
0.1235	0.9691	0.7876	0.823	0.875	125.6	7.19E-12	0.72	0.3071	0.6452
H-bond donor		0.027	Hydrophobic/non-polar		0.535				

Table no. 3 Actual and predicted activities of the training set molecules

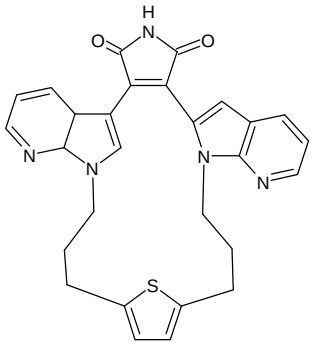
S.No.	Entry ID	Actual activity	Predicted Activity
3	152	8.481	8.41982
4	153	7.886	7.78211
5	154	7.347	7.32871
6	155	7.569	7.78211
7	156	7.481	7.4459
8	157	8.824	8.85539
9	158	8.959	8.97832
11	160	8.569	8.73724
12	161	8.495	8.5564
14	163	9.046	8.99714
16	165	8.921	8.7926
17	166	8.678	8.7648
18	167	8.796	8.76502
19	168	8.328	8.38367
21	170	8.886	8.90404
22	171	9.135	9.20771
24	173	9.097	8.93397
25	174	7.921	7.96463
26	175	8.319	8.10802
28	177	7.222	7.37796
30	179	7.57	7.44445

Table no. 4 Actual and predicted activities of the test set molecules

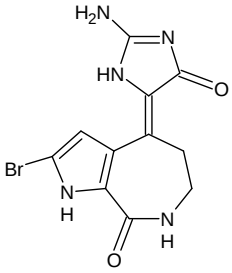
S.No.	Entry ID	Actual activity	Predicted Activity
1	150	8.469	7.78991
2	151	7.387	8.13964
10	159	7.751	8.80057
13	162	8.495	8.11106
15	164	9	8.76782
20	169	8.886	8.66891
23	172	8.72	8.77668
27	176	6.481	7.79186
29	178	6.921	7.64688



Bisindolyl maleimide



Azaindolyl maleimide



Hymenaldisine

Fig no. 1 some promising classes of GSK3β inhibitors.

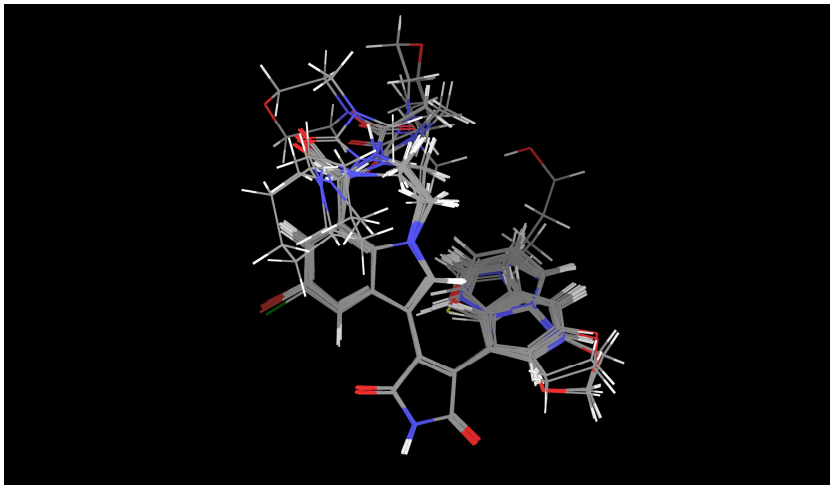
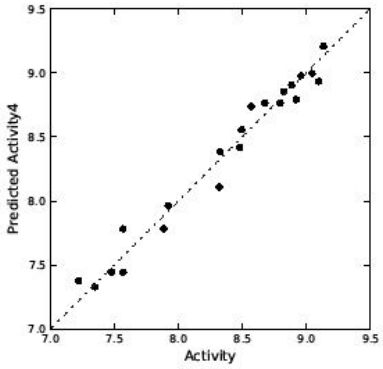


Fig no. 2 Image of molecular alignment



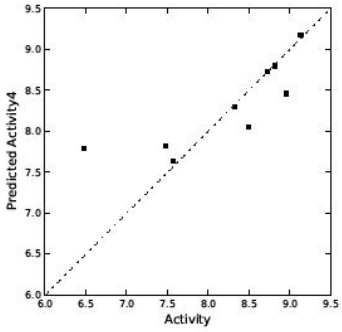


Fig no. 3 Scatter -plot of actual verses predicted activity for training set molecules

Fig no. 4 Scatter -plot of actual verses predicted activity for test set molecules.

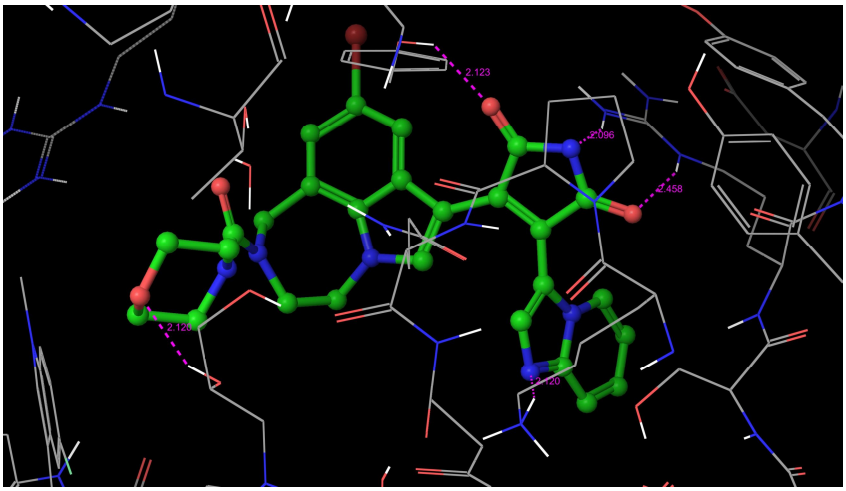


Fig no. 5 Docking image of compound 22 in to active site of GSK3β protein (pdb i.d.1R0E)

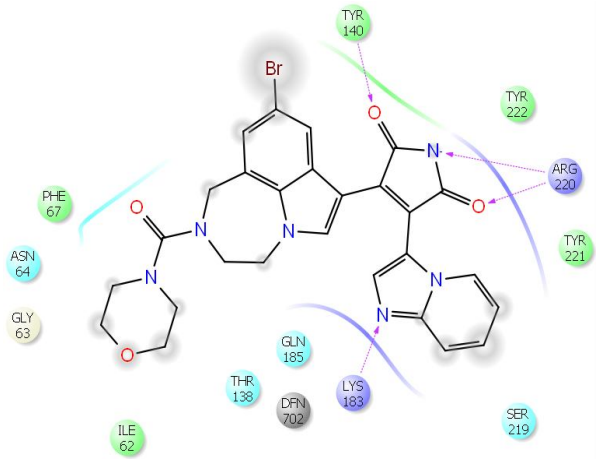


Fig no. 6 Interaction image of compound 22 in to active site of GSK3β protein (pdb i.d. 1R0E).

In order to further investigate the relationship between virtual receptor ligand interactions of the new compounds with their activity. Molecular modeling studies were performed using the crystal structure of gsk3β (pdb.Id.1R0E) domain from protein data bank. The most active molecules (30) were docked in to the active site using glide (Schrodinger 9.3). The active site of protein along with the docked molecules was shown in fig.5. Docking analysis revealed that hydrogen bond interaction and hydrophobic interaction were key factors affecting inhibitory action of the compounds. It displayed vital hydrogen bonding interactions with ARG220, LYS85, and GLU97. The hydrophobic interaction between Val87 and GLU89, the respective interaction image of compound 22 was shown in fig 6.

CONCLUSION

The GSK3β represent a promising target and designing of gsk3β inhibitors would offer a novel approach to develop potent inhibitors. In the current study 30 compounds of bisarylmaleimide series with different structural features were selected to develop a 3D-QSAR models and the selectivity of compounds for developed models were further investigated by molecular docking studies. The analysis of selected models revealed the structural need for the observed selectivity of kinase inhibition. Taken together this could help further design of compounds with an enhanced activity or to guide the prioritization of potential druggables for the purpose of synthesis and virtual screening of chemical database, more work in this area will be required to further substantiate its application on a diverse set of receptors.

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