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RELATIONSHIP BETWEEN SCORING FUNCTION AND THE IC 50 INHIBITORY OF PI3K INHIBITORS

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Abstract

In this study we have made an attempt to find relationship between molecular docking scoring function and the IC 50 inhibitory potency. For this work we have performed Insilico docking studies of five known PI3K inhibitors-GDC-0941, GDC-0980, GSK2146458, BKM-120 and CHN-517385 on PI3K gamma crystal Structure using software Ligandfit and Autodock.

This prediction may help in structure based drug design studies and in selection of designed analogues.

Keyword: PI3K, Molecular docking, Autodock, Ligandfit & Invitro studies, IC50 values.

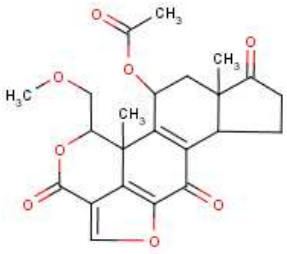
Introduction

PI3Ks target, which is almost 20 years old, was first identified in the literature in 1990. It poses a big challenge for medicinal chemist to come up with some novel designs for targeting this protein. PI3K also known as "Phosphoinositide 3- kinase". PI3Ks come in two parts, a regulatory component and a catalytic component. The two must pair up (heterodimerize) in order to work. PI3Ks do not protrude through the cell membrane; instead they are entirely within the cell and migrate between the cell surface and the cell interior, PI3Ks comprise a group of about 15 proteins with very similar structures[1], The PI3K enzymes are made up of two parts, a regulatory subunit and a catalytic subunit known as p110, of which there are four types (isoforms) - p110 alpha, p110 beta, p110 gamma and p110 delta.

The past 4-5 years have witnessed an explosion of information about small molecules that target the PI3K family. The continuous effort in this area has already resulted at least15 new chemical classes of inhibitors, which are at various stage of clinical studies. Various companies are trying their luck in this field and we can hope for number of PI3K inhibitors in near future.

History PI3K inhibitors: If we go through the history of PI3K inhibitors we will find that the most notable example for PI3K inhibitor is wortamannin and LYS29400217.

Wortmannin, a furanosteroid metabolite of the fungi Penicillium funiculosum and Talaromyces (Penicillium) wortmannii[2], is a specific, covalent inhibitor of phosphoinositide 3-kinases (PI3Ks). Actually wortmannin and LY29400217 (Figure1) were the first set of PI3K inhibitors, but because of their toxicity and lack of selectivity with respect to targets other than class I PI3K family members have limited their therapeutic potential. Although the discovery of wortmannin and LYS2900217 was critical leading to an important pathway for the development of PI3K inhibitors.



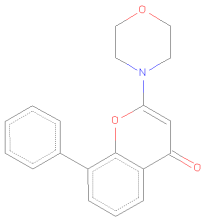


Fig 1. Wortmannin **LY29400217**

The computational docking method is used for designing new analogues and to get insight into protein ligand binding pocket. In our study we have used two docking tools- Ligandfit and Autodock in order to seek new insights into the relationship between scoring function and the IC 50 inhibitory.

The main aim of docking studies is to get an insight into receptor- ligand binding sites. We found it interesting to compare the docking score functions and their experimental IC 50 values for the set of PI3K inhibitors. We have tried to investigate whether we can conclude something from scoring value and its correlation with IC 50 Values for a set of inhibitors such a of study will be very useful for rational design.

Comparisons of binding sites

First of all we to delete compared the binding pocket of PDB ID - 3DBS, 3L08, 3APC, 3TL5, 3SD5 using pymol software. All above five named PDB ID were superimposed one above other, indicating the binding pocket is same for GDC-0941, GDC-0980, GSk2124568, BKM-120, CHN5123458.

Based on our studies we have selected the PDB ID 3DBS for our docking studies. The fig-1 depicts how all the different five PI3K inhibitors are fitting in same binding pocket.

Fig-2: Superimposition of PDB 3 D structures.

Materials and Methods

We have performed docking studies of below listed inhibitors which are various stages of clinical studies using docking software autodock vina and discovery studio - ligandfit.

Autodock: The structure of PI3K gamma protein (PDB ID - 3DBS) was retrieved from PDB. Then all the selected known PI3K inhibitors were docked by using software Autodock and the scores values are predicted. The protein ligand interaction was also studied. All the inhibitors were drawn using symx. To perform the task, genetic algorithm method implemented in the program autodock was employed.

The grid dimension were with points separated by 0.375 A. For all ligands, random starting position and random torsions were used.

Ligandfit: The above inhibitors were docked with discovery studio ligandfit module. ligandfit provides structure based design capabilities including binding site identification & flexible docking and scoring capabilities, allowing evaluation of compounds against a receptor. The automatic docking of a flexible ligand into a protein active site is a critical step in

the process of structure-based design. Ligand Fit provides structure-based design capabilities including binding site finding and flexible docking and scoring capabilities, allowing evaluation of compounds against a receptor site. It is based on Eraser algorithm.

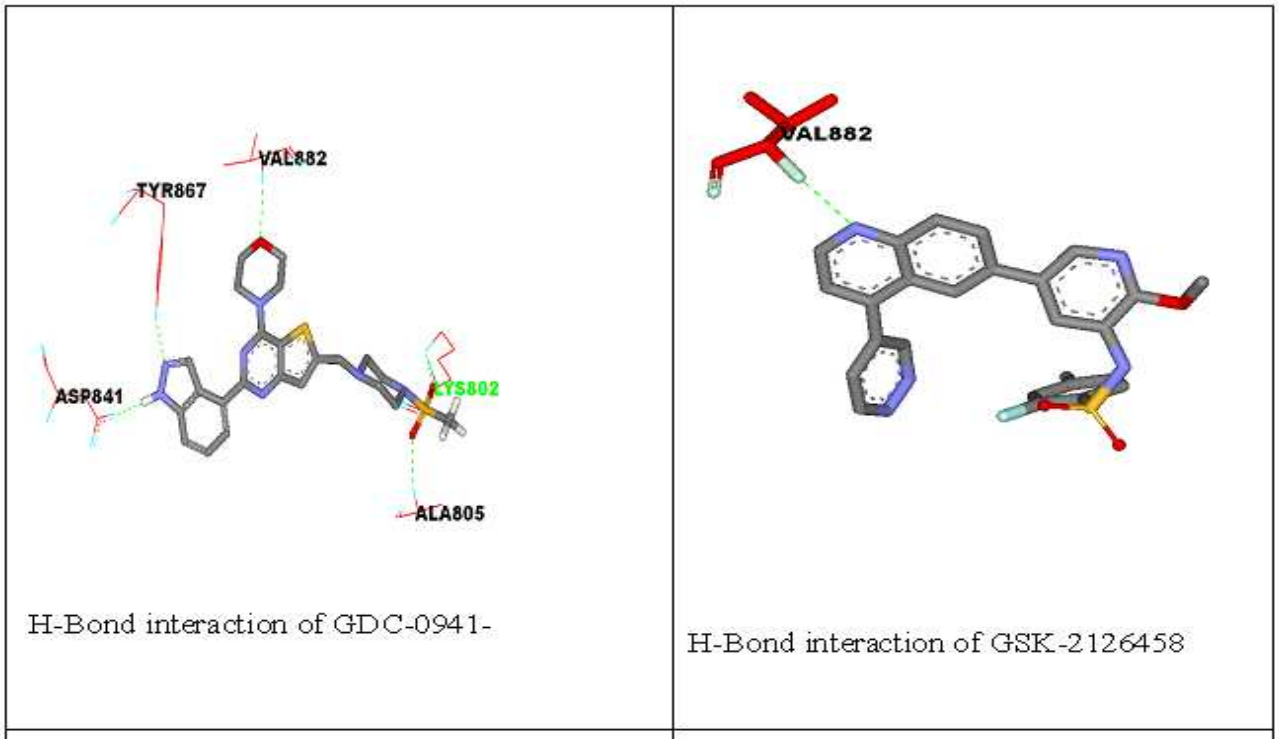
Results and discussion

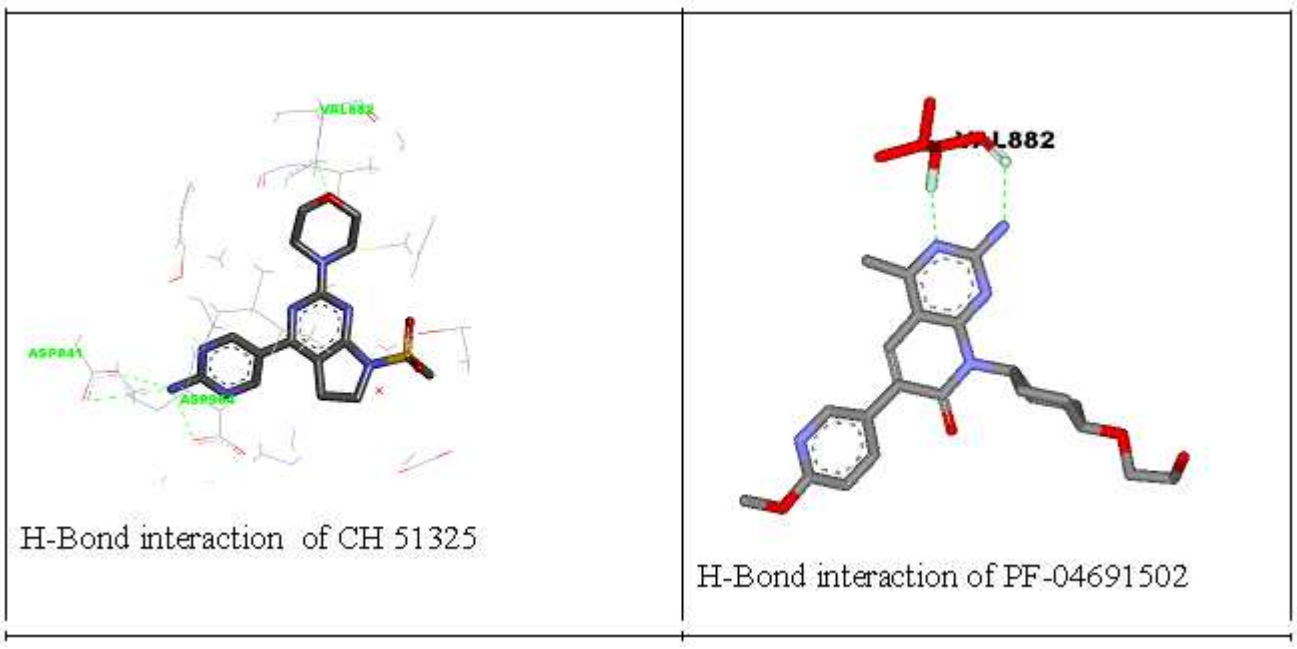
Selected PI3k inhibitors were docked using Autodock and Ligandfit software and docked scores of these molecules were represented in table -1 and Table-2, with their activity, number of hydrogen bonds & interacting residues.

Docking results of the binding orientation and interactions of each PI3K inhibitors for with the active site PI3K as shown in Fig. 3 As we can see from the docking pic that VAL –882 is playing an important role in all five inhibitors.

GDC-0941 is having interaction with Val-882 (the hinge region), ASP-841, TYR-867, Lys-802, Ala-805. On the other hand GSK-2126458 have interaction with Val-882, but others interactions are missing, even same is other inhibitors. This study indicated the importance VAL-882 interaction for PI3k inhibitors. Even we have checked the same with BEZ-235, Novartis molecule, for which Crystal Structure is not available. We have docked this on both PI3K gamma (PDB ID – 3DBS) and P13K alpha (PDB ID – 2RD0).

Fig-3 Docking Models of some representative PI3K inhibitors, highlighting the most important interaction between the inhibitors and The ATP binding pocket.





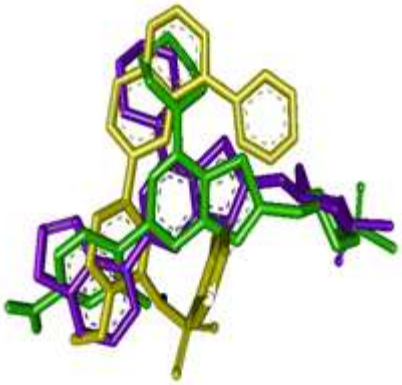
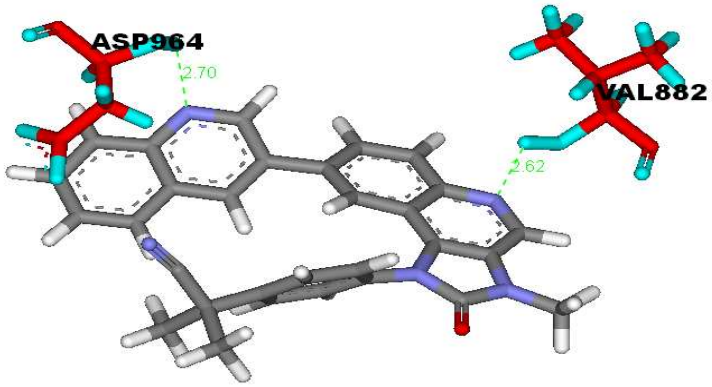


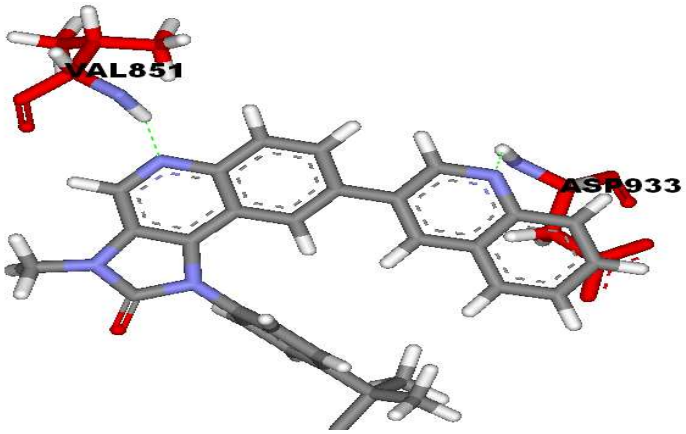
Fig-4: Yellow GSK2126458, green- GDC-0980,Blue- GDC-0941

Structure of PI3K gamma in complex with GDC-0941(PDB ID - 3DB)

Docking Models of BEZ-235, highlighting the most important interaction between the inhibitors and The ATP binding pocket

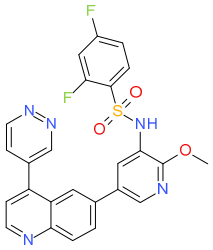
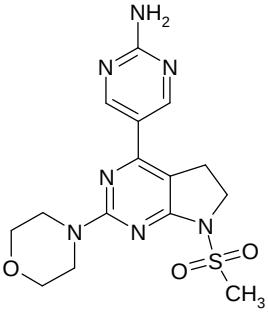


H-Bond Interaction of BEZ-235 docked in PI3K Gamma protein (PDB ID –3DBS)



H-Bond Interaction of BEZ-235 docked in PI3K Alpha protein (PDB ID –2RDO)

Table -1 The structure of PI3K inhibitors using as test set, their IC50 values.

GSK-2126458 (PDB –ID – 3L08)		CH5132799 (PDB ID – 3APC)	
 Company – GSK		 Company – Chugai Pharma	
PI3Kα	0.04nM,	PI3Kα	14 nM,

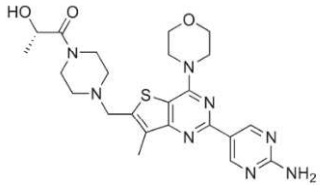
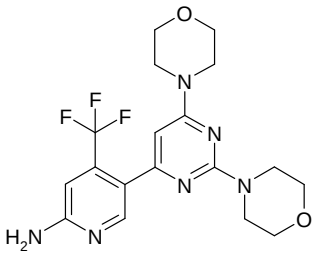
PI3K β	0.13nM,	PI3K β	120 nM,
PI3K γ	0.024M,	PI3K γ	500nM,
PI3K δ	0.6 nM	PI3K δ	360 nM
mTORC1 mTORC2	0.18nM 0.3nM	m TOR	14 nM,
GDC-0980(PDB-ID – 3TL5)  Company – Genentech		BKM-120(PDB ID – 3SD5)  Company Name - Novartis	
PI3Kα	4.8 nM	50 to 300 nM	
PI3K β	27 nM		
PI3K γ	14 nM		
PI3K δ	6.7 nM		
m TOR	17 nM		

Table-2: Scoring Table (ligandfit).

Molecule	Scoring Value				H-Bond Residues
	PLP1	PLP2	LigScore2	D-Score	
GDC 0941 (ref)	118.34	112.02	7	112.601	VAL 882,LYS 802,ALA 805, TYR 867, ASP 841
GSK	105.33	97.66	5.5	101.617	VAL 882,ASP 964
CH 513245	89.11	77.02	6.02	85.119	VAL 882,ASP 964
GDC-0980	110.37	102.26	6.4	105.402	VAL 882,LYS 802,ALA 805, ASP 841,ASP 964
BKM-120	94.28	79.89	2.95	89.474	VAL 882,TYR 867, ASP 841

Scoring Table (Autodock)

SL No	Molecule	H bond residues	Binding affinity
1	GDC0941	VAL 882 –1.83 TYR867 –2.43 ASP 841 –1.95 LYS 802 –2.09 ALA 805 –2.33	-8.92
2	GSK	VAL 882 –1.94 ASP 964 –2.08 LYS 833 –2.09	-10.03
3	CH 513245	VAL 882 –1.79 ASP 964 –2.29 ASP 841 –1.70	-7.61
4	GDC-0980	VAL 882 –1.59 ASP 964 –2.81 ASP 841 –2.42 LYS 802 –2.46 ALA 805 –2.23	-7.26
5	BKM-120	VAL 882 –1.67 ASP 836 –2.23	-6.75

For easy comparison of experimental and calculated values we have listed IC50 values as per literature in Table-1.

Conclusion

The predicted scoring value was used as criteria for ranking. The best docking score was obtained for GSK molecule by both software which correlated with IC50 values.

The Scoring function is considered as an initial criterion to estimate the binding affinity of a PI3K inhibitor. The results show significant correlation between Scoring function and pIC50 values. As we can see that GSK compound is having the best activity in terms of IC 50 values and in terms of scoring also it is having better binding activity. Both docking score is indicating the same result. This approach of binding affinities of compounds. Can be used for designing new analogues.

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Reference

1. http://www.liferaftgroup.org/news_sci_articles/PI3Ks.html.
2. Source: www.fermentek.co.il/wortmannin.htm.
3. Hayakawa, M.; Kaizawa, H.; Moritomo, H.; Koizumi, T.; Ohishi, T.;Okada, M.; Ohta, M.; Tsukamoto, S.; Parker, P.; Workman, P.;Waterfield, M. Synthesis and biological evaluation of 4-morpholino-2-phenylquinazolines and related derivatives as novel PI3 kinase p110R inhibitors. *Biorg. Med. Chem*. 2006, *14*, 6847–685.
4. Identification and characterization of NVP-BEZ235,a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. Mol Cancer Ther 2008; 7(7). July 2008.
5. Chemically targeting the PI3K family. Knight and K.M. Shokat1 Howard Hughes Medical Institute, Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA, U.S.A..
6. The Identification of 2-(1*H*-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno [3,2-*d*]pyrimidine (GDC-0941) as a Potent, Selective, Orally BioavailableInhibitor of Class I PI3 Kinase for the Treatment of Cancer 10.1021/jm800295d.

7. Journal of Molecular Graphics and Modelling 29 (2010) 425–435.

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