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Essence of Inhibitor Design Unveiled: Real Time Structural Analysis of Epidermal Growth Factor Surface Receptors in Pancreatic Cancer Drug Discovery – Incubation Science in Therapeutics?

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Abstract

Targeting protein molecule present inside the cancerous cell is the new fashion of therapeutic approach in cancer drug discovery programs. One appealing and well-known molecular target is epidermal growth factor receptor (EGFR). Blocking the EGFR through small molecules has considered being to be one of the ideal methods to diminish the progression of the cancer in humans and that would primarily overlays the basis for the development of anti-EGFR molecules. Though full-fledged anti-EGFR molecules already exist, the need for toxic free and selective inhibitors is the active area of research going on now. This study is an effort to develop unprecedented and potent lead molecules. We screened susceptible molecules from Zinc database to find so. Finally, we got five molecules that are highly recommendable for pancreatic cancer, in addition to that pharmacokinetics properties purely comes under the range of valid figures. This sets a promise that reported five molecules could be successful molecules to be tested in *invitro* and *invivo* settings.

Key-Words: Pancreatic Cancer, EGFR, Glide, ADME.

Introduction

Pancreatic cancer is one of the leading cancers with estimated probable cases of 48,960 (24, 840 men and 24,120 women) in the United States. It is estimated that 40,560 deaths (20, 710 men and 19, 850 women) from this disease will occur in 2015 [1].The epidermal growth factor receptor is a trans membrane glycoprotein belongs to the erbB family [2, 3]. The epidermal growth factor receptor is known to interact with a number of endogenous ligands like EGF, TGF-α, as these ligands bind in a sequential manner, which results in the conformational change. The change in the confirmation leads to the intrinsic catalytic activity of a tyrosine kinase and result in autophosphorylation and without further delay accelerates the biological activity. Its role in cell is phenomenal that ranges from cell proliferation, survival, adhesion, migration, and differentiation and signal transduction pathways [4-6].

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The sudden changes in the nuclear arrangement of EGFR gene results in the overexpression of activity that results in the genesis of several cancer types, especially pancreatic cancer [7].Hence, our attention started by studying the molecular aspects of EGFR, which further allowed to screen 1,32,000 to filter lead like molecules. The well known methods such as energy based molecular docking and ADME prediction are carried out to identify potent inhibitors of EGFR.

Material and Methods

Structure based virtual screening

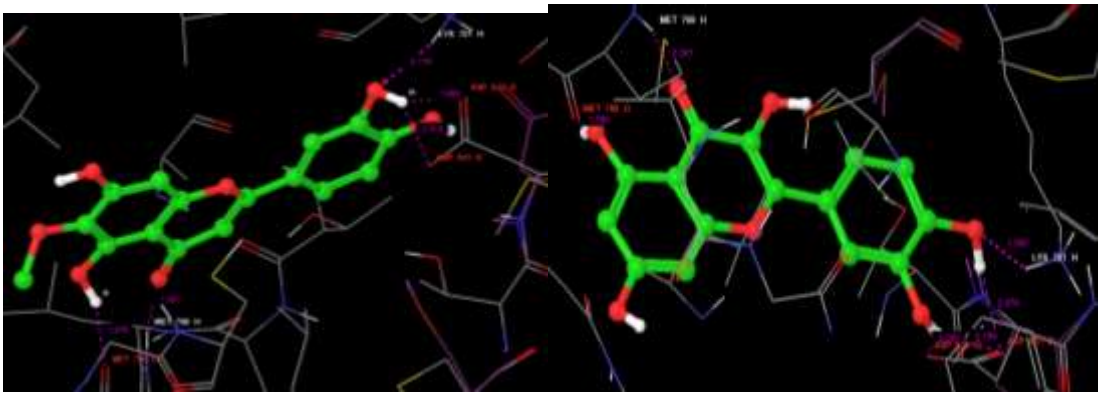
This study was carried out with the assitance of ubiquitous docking algorithm, glide version 6.0 [8] for find the binding preference of unknown ligands that are to be screened against the target. The EGF receptor crystal structure was picked from protein databank (PDB ID:1M17) [9] with a resolution factor of 2.60Å. Cleaning up the protein is the foremost thing before moving into the docking analysis. The usual treatment that protein molecule undergoes during protein preparation is that, water molecules and co-crystal

liagnd was removed, hydrogen atom were added to retain the tautomeric and ionization state of aminoacid, followed by that energy was minized using OPLS-2005 [10].Next step would be the generation of the grid, the grid generation is confined to the region where the co-crystal was found, by then the actuall binding efficiency of new ligands could be easily analyzed. To identify inhibitors against the above processed EGFR, flexible ligand based high-throughput virtual screening (HTVS) mode of Glide 6.0 was carried out using 1,32,000 molecules of commercially available plant chemical compounds from the Zinc [zinc.docking.org]. Another worth step in protein- ligand docking is ligand preparation. Ligand preparation is done by ligprep version 2.7,converts 3D structure from 2D structure, include different tautomers and ionized form at a pH range 7.0± 2.0 [11].Later ligands were taken to the docking process. Initial docking analysis is done with the help of high throughput screening (HTVS), secondly standard precison (SP)mode and all the obtained molecules were subjected to the Glide extra precision (XP) mode of docking, which performs extensive sampling and provides reasonable binding poses.The essence of efficacy of ligand molecules is determined by the behavior of them in the human biological system, which is validated by several pharmacokinetics parameters. Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, calculated using QikProp version 3.7 [12].

Results and Discussion

To start with, we selected 1, 32, 000 compounds from the public ligand database named ZINC. Then, by the means of high throughput virtual screening (HTVS) and standard-precision mode , 5,000 molecules were obtained based on the glide score. Same strategy with Glide extra-precision mode yielded five molecule posssesed better glide score when compared to co-crystal ligand erlotinib. Five molecules significantly satisfy the pharmacokinetic factors that are defined for human use and qualify as potential drug like molecules. They are: ZINC95486342:(2S,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3S,4S,5R)-3,4,5-trihydroxytetrahydropyran-2-yl];ZINC03869685:Quercetin;ZINC05998557:2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-6-methoxy-4H-chromen-4-one;ZINC14641685:KenusanoneB; ZINC5842416: Scutellarein.The interacting residues for these lead molecules are shown in Table 1 and their 2d structures are shown in Fig. 2.The pharmacokinetic properties of the five ligands were assessed by the use of Qikprop were reported in table 2. The above five lead molecules fulfill drug-like properties based on Lipinski's rule of five. The molecular weight of the lead molecules are less than 500 kDa, number of hydrogen bond donors is less than 5 and hydrogen bond acceptors are less than 10. The predicted octanol/water partition coefficient (QPlogPo/w) is in the acceptable range i.e. 3.553 to -0.788, QP log BB for brain/blood ranges i. e. -1.782 to -2.975. The binding pose of the selected five lead molecules is illustrated in Fig. 1, of whichZINC95486342 compound possess better glide score when compare to the other compounds

ZINC05998557 ZINC03869685



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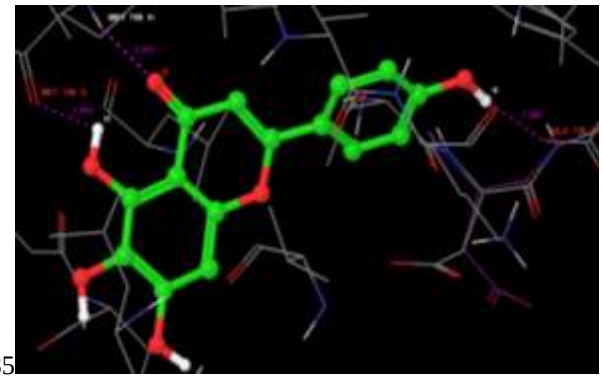

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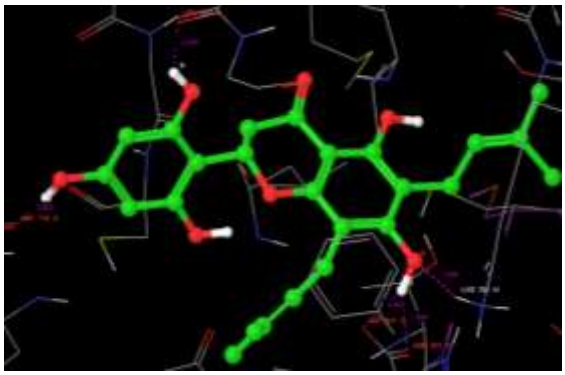

ZINC95486342

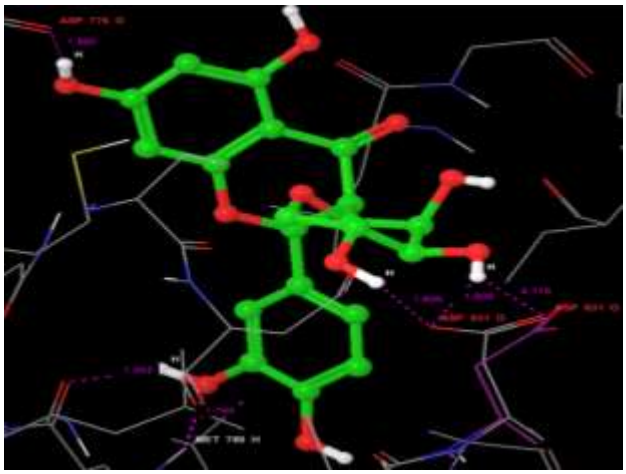

Figure1: Binding pose of five natural compounds.

Table1: Glide extra-precision (XP) results for five molecules by use of Schrodinger 9.5.

Compound ID	Glide score(Kcal/mol)	Glide energy(Kcal/mol)	No of H_2 bonds	Interacting residues
Zinc 95486342	-10.0217	-44.518	6	MET 796, ASP 776, ASP 831
Zinc 03869685	-9.532	-41.883	6	MET 769, LYS 721, ASP 831
Zinc 05998557	-9.909	-44.335	5	MET 769, LYS 721, ASP 831
Zinc 14641685	-6.038	-49.782	5	THR 766, LEU 694, LYS 721, ASP 831
Zinc 5842416	-7.630	-39.576	3	MET 769, GLU 738

Table 2: The ADME properties of the ten natural compounds were predicted using Qikprop.

Compound ID	MW	HBD	HBA	$Log_{P\ (o/w)}$	QPLogB/B
ZINC95486342	420.372	6.000	11.550	-0.788	-2.975
ZINC03869685	302.240	4.000	5.250	0.391	-2.298
ZINC05998557	316.267	3.000	5.250	1.113	-1.782
ZINC14641685	440.492	4.000	5.500	3.553	-2.056
ZINC5842416	286.240	3.000	4.500	1.015	-1.868

Solute Molecular Weight = 368.385 (130.0 / 725.0)
Solute as Donor - Hydrogen Bonds = 3.000 (0.0 / 6.0)
Solute as Acceptor - Hydrogen Bonds = 4.500 (2.0 / 20.0)
QP log P for octanol/water = 3.073 (-2.0 / 6.5)
QP log BB for brain/blood = -1.962 (-3.0 / 1.2)

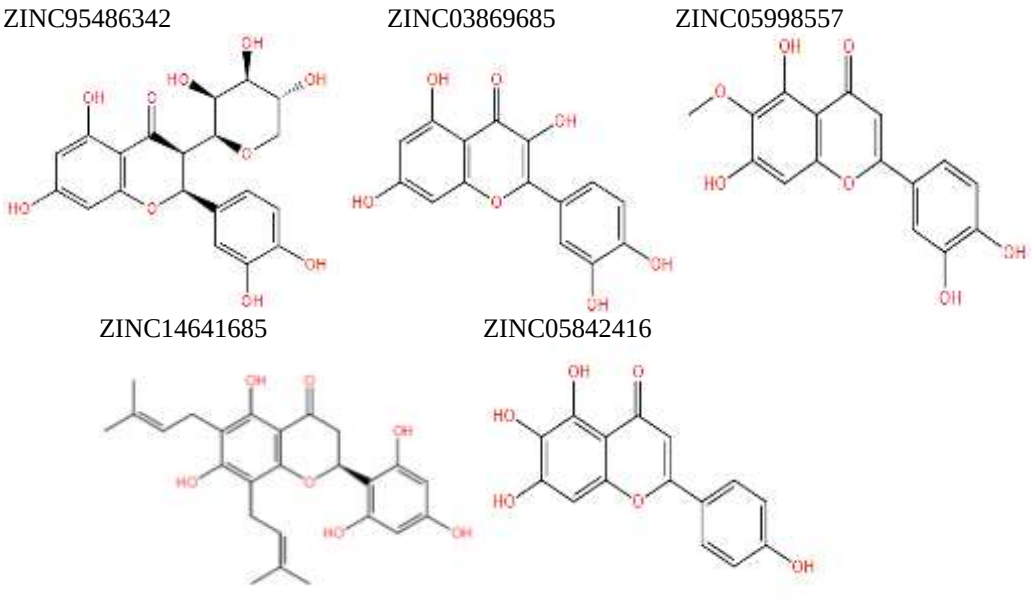

Figure 2: 2D structure of the five natural compounds.

Conclusion

Pancreatic cancer is a leading cancer type. Devoid ofless toxic and selective multi-faceted blockbusters drugs, propelled us to initiate this study. This study is an improvised and structured method where we can engage in using molecular docking tool and pharmacokinetics prediction to figure out lead- like molecules. At last, we are successful enough to find top five molecules. We believe this can be a lead for the core objective of the study to further subject them to *invitro* and *invivo* analysis.

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